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INTRAOCULAR HEMORRHAGE IN CATARACT EXTRACTION

WILLIAM COUNCILMAN OWENS, M.D.
AND
WILLIAM F. HUGHES Jr., M.D.
BALTIMORE

THE LITERATURE on intraocular hemorrhage associated with cataract extraction has been reviewed at length by various authors, and the possible causes of this complication have been widely discussed.[1] The majority of the reports lack sufficient data to permit a statistical analysis of etiologic factors and adequate deduction of prophylactic measures. Therefore, we have reviewed the material which formed the basis of our former report [2]—i. e., 2,086 extractions of uncomplicated senile cataract performed at the Wilmer Ophthalmological Institute

From the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital and University.

Read at a meeting of the New York Academy of Medicine, Section of Ophthalmology, March 18, 1946.

1. (*a*) DeVoe, G.: Hemorrhage After Cataract Extraction, Arch. Ophth. **28**:1069 (Dec.) 1942 (bibliography before 1943). (*b*) Broman, T.: On the Occurrence of Iritis After the Extraction of a Cataract, Acta ophth. **14**:170, 1936. (*c*) Purtscher, E., and Dibold, H.: Zur intrakapsulären Starextraktion beim Diabetiker, Klin. Monatsbl. f. Augenh. **98**:24, 1937. (*d*) Meyer, F. W.: Ueber die postoperative Nachblutung nach Starextraktion und ihre Ursachen, ibid. **102**: 479, 1939. (*e*) Kotz, H.: Nachblutungen nach Altersstaroperationen, ibid. **108**: 291, 1942. (*f*) Gradle, H. S., and Sugar, H. S.: Wound Rupture After Cataract Extraction, Am. J. Ophth. **25**:426, 1942. (*g*) Klein, M.: Operation for Cataract, Brit. J. Ophth. **26**:93, 1942. (*h*) McArevey, J. B.: Postoperative Hemorrhages, Tr. Ophth. Soc. U. Kingdom **63**:407, 1943. (*i*) Davis, F. A.: Intracapsular Cataract Extraction, Arch. Ophth. **31**:367 (May) 1944. (*j*) Kirby, D. B.: Further Experiences with a System of Intracapsular Extraction of Cataract, ibid. **31**:302 (April) 1944. (*k*) Dunnington, J. H.: Some Complications of Cataract Extraction, New York State J. Med. **44**:2224, 1944. (*l*) Mathewson, W. R.: Vitamin P in Ophthalmology, Brit. J. Ophth. **28**:336, 1944. (*m*) Mann, I.: Effect of Ascorbic Acid on the Occurrence of Hyphema After Cataract Extraction, ibid. **29**:175, 1945. (*n*) Neff, E.: Factors Affecting Hemorrhage Following Cataract Extraction, Arch. Ophth. **33**:192 (March) 1945. (*o*) Atkinson, W. S.: Preliminary Report of Corneal Section with Long Bevel and Conjunctival Flap for Cataract Extraction, Tr. Am. Ophth. Soc. **43**:97, 1945.

2. Hughes, W. F., Jr., and Owens, W. C.: The Extraction of Senile Cataract: A Statistical Comparison of Various Techniques and the Importance of Preoperative Survey, Am. J. Ophth. **28**:40, 1945.

between November 1925 and October 1943—for any information it might yield on ocular hemorrhage. The results are analyzed statistically, and no factor is considered significant unless the probability of chance is less than 1 in 20 ($p = 0.05$).

In the study of this problem, we have asked ourselves the following questions: 1. What factors in the patient's physical status or in the operative technic produce intraocular hemorrhage? 2. How may these factors be controlled or altered to prevent this complication? 3. What effect does each type of hemorrhage have on the postoperative course and the final visual results?

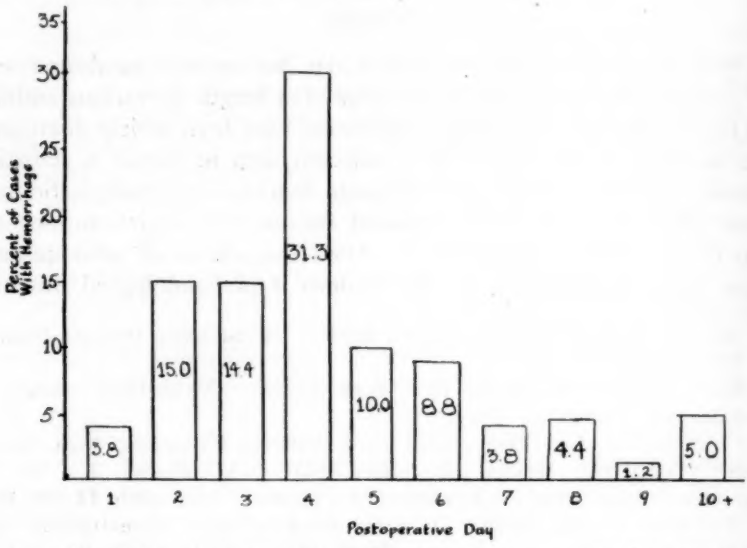

Chart 1.—Onset of postoperative hemorrhage into the anterior chamber.

Three types of intraocular hemorrhage are evaluated in this study: (1) postoperative hemorrhage into the anterior chamber, (2) hemorrhage into the anterior chamber occurring at the time of operation and (3) expulsive, or subchoroidal, hemorrhage.

POSTOPERATIVE HEMORRHAGE INTO THE ANTERIOR CHAMBER

Incidence.—Differences in the reported incidence of postoperative hemorrhage into the anterior chamber are probably due to variations in definition. In this study, fresh bleeding seen at the time of the first dressing or at subsequent dressings was defined as postoperative hemorrhage into the anterior chamber. Flecks of blood, occasionally noted at the first dressing, were probably residua of hemorrhage at the time of operation and were not considered postoperative hemorrhage. Postoperative hemorrhage occurred in 195 cases (9.3 per cent). In 71 of

these (3.6 per cent) the hemorrhages were designated as "severe" because they either filled the anterior chamber completely or were recurrent.

Time of Onset.—In this series, the usual period for the occurrence of postoperative hemorrhage into the anterior chamber was between the second and the sixth day after operation (chart 1). This is in accord with the figures of other reports.

Duration.—The blood was completely absorbed from the anterior chamber during the first seven days after the appearance of the hemorrhage in 78.9 per cent of the cases with mild hemorrhage but in only 43.3 per cent of the cases with severe hemorrhage (chart 2).

TABLE 1.—*Effect of Age on Postoperative Hemorrhage into Anterior Chamber*

Age, Yr.	No. of Cases	Postoperative Hemorrhage into Anterior Chamber, per Cent
Less than 50	211	11.4
50 to 59	475	11.6
60 to 69	760	9.2
70 to 79	547	8.1
Over 80	91	9.9

SYSTEMIC FACTORS PRODUCING POSTOPERATIVE HEMORRHAGE INTO THE ANTERIOR CHAMBER

In order to determine what factors in the patient's general physical status might predispose to the occurrence of postoperative hemorrhage into the anterior chamber, the cases were analyzed from the following standpoints: (1) age, (2) blood pressure, (3) blood-clotting mechanisms, (4) diabetes, (5) syphilis and (6) foci of infection.

Age.—The age of the patient had no relation to the occurrence of postoperative hemorrhage into the anterior chamber (table 1).

TABLE 2.—*Effect of Blood Pressure on Postoperative Hemorrhage into Anterior Chamber*

Systolic Blood Pressure, Mm. Hg	No. of Cases	Postoperative Hemorrhage into Anterior Chamber, per Cent	Diastolic Blood Pressure, Mm. Hg	No. of Cases	Postoperative Hemorrhage into Anterior Chamber, per Cent
Less than 120	164	11.0	Less than 70	128	9.4
120 to 139	457	8.3	70 to 79	381	9.6
140 to 159	559	10.4	80 to 89	641	10.6
160 to 179	389	8.4	90 to 99	496	9.7
180 to 199	294	9.8	100 to 109	223	4.5
200 to 219	136	11.8	Over 110	185	11.9
Over 220	75	10.4			

Blood Pressure.—Hypertension has been considered an important cause of postoperative hemorrhage into the anterior chamber. In this series, the occurrence of postoperative hemorrhage was completely independent of the patient's systolic or diastolic blood pressure. In patients with systolic pressure of from 120 to over 200 mm. of mercury, the

percentage of occurrence varied only from 8.3 to 11.8. In patients with diastolic pressure of from 70 to over 110 mm. of mercury, the percentage of occurrence was between 4.5 and 11.9, the low incidence occurring in patients with a diastolic pressure of 100 to 109 mm. (table 2).

Blood-Clotting Mechanism.—A low prothrombin level has been considered a cause of hemorrhage into the anterior chamber, although Quick [3] and others have shown that 80 per cent of the serum prothrombin can be lost before the coagulation time is appreciably prolonged and a hemorrhagic tendency develops. Foss, DeVoe and Davis [4] found no relation between the occurrence of postoperative hemorrhage and the

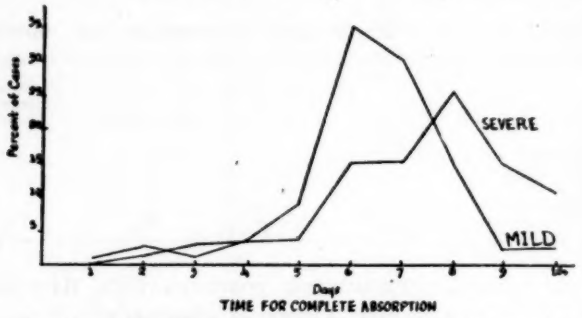

Chart 2.—Duration of postoperative hemorrhage into the anterior chamber.

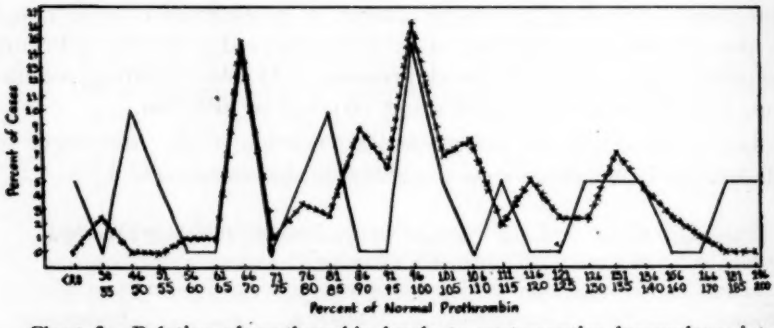

Chart 3.—Relation of prothrombin levels to postoperative hemorrhage into the anterior chamber. Values for the cases with hemorrhage are indicated by the solid line; values for the cases without hemorrhage, by the line with crosses.

plasma prothrombin level. In 133 of our cases in which the plasma prothrombin level was determined by the method of Warner, Brinkhous and Smith [5] no significant relationship was found between the pro-

3. Quick, A. J.: A Classification of Hemorrhagic Disease Due to Defects in the Coagulation Mechanism of the Blood, Am. J. M. Sc. **199**:118, 1940.

4. Foss, B.: Gibt es eine K-Vitamininsufficienz bei Blutungen nach intrabulbaren Eingriffen? Acta ophth. **19**:15, 1941. DeVoe.[1a] Davis.[11]

5. Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: A Quantitative Study on Blood Clotting: Prothrombin Fluctuations Under Experimental Conditions, Am. J. Physiol. **114**:667, 1936.

thrombin levels and postoperative hemorrhage (chart 3). In only 1 case was the prothrombin level less than 20 per cent of normal, which Quick has stated as the critical level. In this case a severe postoperative hemorrhage occurred. However, when a cataract extraction was performed on this patient's other eye one year later, the prothrombin level was 99 per cent of normal, and the patient had been under prophylactic treatment with vitamin K. In spite of this, the second operation was followed by a severe hemorrhage.

TABLE 3.—*Effect of Severity of Diabetes on Severe Postoperative Hemorrhage into Anterior Chamber*

Severity of Diabetes	No. of Cases	Severe Hemorrhage into Anterior Chamber, per Cent
Duration less than 9 yr.	166	1.8
Duration 9 yr. or more	58	10.4
Insulin per day less than 30 units	169	1.8
Insulin per day 30 units or more	55	10.9
Duration 9 yr. or more and insulin per day 30 units or more	19	21.0

The clotting time was measured by the standard tube method in 50 cases with postoperative hemorrhage into the anterior chamber and in 46 cases without postoperative hemorrhage. In all these cases the clotting time was less than fifteen minutes, the upper limit of normal with this method.

Diabetes.—Postoperative hemorrhage into the anterior chamber occurred in 12.4 per cent of 235 cases with diabetes and in 9.2 per cent of 1,852 cases without diabetes. Although suggestive of a correlation between the presence of diabetes and hemorrhage, this over-all observed

TABLE 4.—*Effect of Blood Sugar Level on Postoperative Hemorrhage into Anterior Chamber*

Highest Preoperative or Postoperative Blood Sugar	No. of Cases	Postoperative Hemorrhage into Anterior Chamber, per Cent
Less than 175 mg./100 cc.	159	13.2
Over 175 mg./100 cc.	63	8.0

difference is not statistically significant. However, patients with diabetes of long standing, or those requiring large amounts of insulin, showed an increased incidence of severe hemorrhage, the incidence rising sharply to 21 per cent in patients with diabetes of over nine years' duration and requiring over 30 units of insulin per day for regulation (table 3). It is interesting that there was no similar relationship between mild postoperative hemorrhage and the duration or severity of diabetes.

There was no significant relationship between the preoperative or postoperative blood sugar level and the occurrence of postoperative

hemorrhage (table 4). Likewise, the diabetic patients with central retinitis had essentially the same incidence of postoperative hemorrhage as those without central retinitis (table 5).

Syphilis.—In this series, there were 64 cases of late latent syphilis with positive serologic reactions and 41 cases of late visceral or neuro-

TABLE 5.—*Relation of Central Retinitis in Diabetic Patients to Postoperative Hemorrhage into Anterior Chamber*

Central Retinitis	No. of Patients	Postoperative Hemorrhage into Anterior Chamber, per Cent
Present	43	11.6
Absent	189	12.7

syphilis. Table 6 shows that the incidence of postoperative hemorrhage into the anterior chamber was essentially the same in the syphilitic patients as in the nonsyphilitic patients.

Foci of Infection.—A thorough preoperative search for foci of infection was made on 1,482 patients. It included a general physical exam-

TABLE 6.—*Effect of Syphilis on Postoperative Hemorrhage into Anterior Chamber*

Syphilis	No. of Cases	Postoperative Hemorrhage into Anterior Chamber, per Cent
Present	105	10.5
Absent	1,947	9.7

ination, routine consultation with an otolaryngologist (usually including roentgenologic studies of the sinuses), dental consultation with roentgenographic studies, consultation with the gynecologic or urologic departments if indicated, a Wassermann test of the blood, urinalysis and often

TABLE 7.—*Effect of Focus of Infection on Postoperative Hemorrhage into Anterior Chamber*

Focus	No. of Cases	Postoperative Hemorrhage into Anterior Chamber, per Cent
Present, inadequate treatment	188	10.7
Present, adequate treatment	188	10.1
Absent	1,106	9.8

tuberculin sensitivity tests and roentgenologic examination of the chest. As a result of this study, 1,106 patients were found free of foci, but definite foci were found in 376 patients. Half the latter group received adequate treatment of the focus before the cataract extraction. The presence or absence of a focus of infection had no relation to the occurrence of postoperative hemorrhage into the anterior chamber (table 7).

FACTORS IN OPERATIVE TECHNIC

An analysis was made of the following factors in the operative technic which might influence the occurrence of postoperative hemorrhage into the anterior chamber: (1) type of cataract extraction, (2) type of operation on the iris, (3) use of sutures and (4) loss of vitreous.

Type of Cataract Extraction.—The cases were divided into three groups, according to the type of extraction: (1) intentional extracapsular

TABLE 8.—*Effect of Type of Extraction on Postoperative Hemorrhage into Anterior Chamber*

Type of Extraction	No. of Cases	Postoperative Hemorrhage into Anterior Chamber, per Cent
Extracapsular	639	8.8
Broken capsule	335	11.9
Intracapsular	1,011	9.3

extraction, (2) attempted intracapsular extraction in which the capsule ruptured during the operation and (3) intracapsular extraction. The observed differences in the occurrence of hemorrhage in these three groups were not large enough to be significant, varying only between 8.8 and 11.9 per cent (table 8).

Use of Sutures.—Four types of closure of the operative wound were used: no sutures, sutures in a pocket conjunctival flap and one or two

TABLE 9.—*Influence of Sutures on Postoperative Hemorrhage into Anterior Chamber*

Sutures	No. of Cases	Hemorrhage into Anterior Chamber, per Cent
None	390	7.7
Conjunctival	629	12.2
Corneoscleral (one)	482	13.3
Corneoscleral (two)	558	4.7

corneoscleral sutures. As may be seen from table 9, the use of two corneoscleral sutures to secure firm closure of the wound decreased the incidence of postoperative hemorrhage. However, the cases without sutures and relatively shallow sections also had a low incidence of postoperative hemorrhage. The shallow sections in this group probably healed with little vascularization. Thus, the ideal section for the reduction of postoperative hemorrhage into the anterior chamber seems to be a shallow one firmly closed with two corneoscleral sutures.

Type of Operation on the Iris.—The cases were divided into groups according to the type of suture used and then subdivided according to the type of operation on the iris. In all groups—those without sutures, those with conjunctival sutures or those with one and two corneoscleral sutures—there was a slight increase in postoperative

hemorrhage when a full iridectomy was performed at the time of operation (table 10). However, this difference was not statistically significant.

Loss of Vitreous.—There was a progressive increase in the incidence of postoperative hemorrhage into the anterior chamber with the loss of increasing amounts of vitreous. The percentage incidence of hemorrhage into the anterior chamber rose from 8.9 in cases without loss of vitreous to 23.9 in cases in which there had been a great loss of vitreous (table 11).

TABLE 10.—*Influence of Sutures and Type of Iridectomy on Postoperative Hemorrhage into Anterior Chamber*

Sutures	Iridectomy	No. of Cases	Hemorrhage, per Cent
None	Full	280	8.1
	Preliminary	107	6.6
Conjunctival	Full	523	14.0
	Preliminary	108	10.7
One corneoscleral	Full	426	14.3
	Round pupil	40	7.5
Two corneoscleral	Full	179	6.1
	Round pupil	374	4.0

TABLE 11.—*Effect of Loss of Vitreous on Postoperative Hemorrhage into Anterior Chamber*

Loss of Vitreous	No. of Cases	Postoperative Hemorrhage into Anterior Chamber, per Cent
None	1,720	8.9
Presentation	154	9.8
Moderate	141	12.0
Severe	46	23.9

TABLE 12.—*Relation of Other Complications to Postoperative Hemorrhage into Anterior Chamber*

Postoperative Hemorrhage into Anterior Chamber	No. of Cases	Incomplete Closure of Wound, per Cent	Delayed Reformation of Anterior Chamber, per Cent	Prolapse of Iris, per Cent	Iridocyclitis, per Cent
Present	195	3.6	1.0	3.6	4.6
Absent	1,891	2.8	1.1	3.3	6.3

OTHER FACTORS

Hemorrhage into the anterior chamber followed the removal of corneoscleral sutures in 3.6 per cent of the cases in which they were used. However, these hemorrhages were mild, cleared uneventfully and had no effect on the final visual results.

No relationship was found between postoperative hemorrhage and visible gaping of the wound, delayed reformation of the anterior chamber, prolapse of the iris or iridocyclitis (table 12).

SUMMARY OF CAUSES OF HEMORRHAGE INTO ANTERIOR CHAMBER

The data given previously have shown that, except for severe diabetes, the general systemic condition of the patient is unrelated to the occurrence of postoperative hemorrhage. So far as operative technic is concerned, the use of two corneoscleral sutures to close the wound more securely was found to be an important factor in reducing the incidence of this complication. Since hemorrhages into the anterior chamber occur most frequently between the second and the sixth postoperative day and are less common in eyes with shallow sections, it is a logical deduction that postoperative hemorrhage results from a rupture of the small capillaries that have grown into the healing incision. In many cases the blood can be seen to arise from the section and trickle into the anterior chamber immediately after minor trauma or after removal of the corneoscleral sutures. When the sutures are deeply placed or the patient is uncooperative, hemorrhage can be prevented by postponing the removal of sutures until the wound is more securely healed. The increased incidence of hemorrhage after loss of vitreous can be attributed to the poor healing of the wound in such cases.

VISUAL RESULTS

The visual results were significantly poorer in the cases of postoperative hemorrhage into the anterior chamber. Table 13 shows that in only 67 per cent of the cases with postoperative hemorrhage was there a visual result of 20/30 or better, while in 81 per cent of the cases without hemorrhage there was a visual result of 20/30 or better. This tabulation includes only those cases in which an adequate refraction had been made and in which there were no causes of poor vision independent of the cataract extraction, such as senile macular degeneration. The major cause of the poor results after hemorrhage was found to be persistent opacities in the vitreous. Such opacities were the primary cause of reduction of vision below 20/30 in 20.2 per cent of the cases in which postoperative hemorrhage occurred, in contrast to 12.2 per cent of cases without hemorrhage. In many of the cases with postoperative hemorrhage into the anterior chamber, a reduction or abolition of the red reflex persisted after absorption of the blood from the anterior chamber. This

TABLE 13.—*Effect of Postoperative Hemorrhage into Anterior Chamber on Visual Result*

Posoperative Hemorrhage into Anterior Chamber	No. of Cases	Visual Results, per Cent		
		20/15 to 20/30	20/40 to 20/70	20/100 or Less
Present	143	67.0	15.4	17.5
Absent	1,336	81.5	8.7	9.9

was probably due to a seepage of blood into the vitreous, where further absorption proceeded slowly and often resulted in persistent opacities in the vitreous. In a few cases blood could be seen in the vitreous in spite of an intact hyaloid membrane.

In some cases with severe hemorrhage into the anterior chamber a membrane persisted over the pupillary space. Even after intracapsular

TABLE 14.—*Relation of Postoperative Hemorrhage into Anterior Chamber to Glaucoma and Phthisis Bulbi*

Postoperative Hemorrhage into Anterior Chamber	No. of Cases	Posoperative Glaucoma, per Cent	Phthisis Bulbi, per Cent
Present	195	5.6	2.6
Absent	1,891	4.3	1.3

extractions, a discission was occasionally necessary. After extracapsular extractions, blood lying on the posterior capsule is absorbed extremely slowly and frequently results in a thick pupillary membrane.

Postoperative hemorrhage did not predispose to late secondary glaucoma or phthisis bulbi (table 14).

HEMORRHAGE INTO THE ANTERIOR CHAMBER OCCURRING AT OPERATION

There were 36 cases in this series in which blood remained in the anterior chamber at the end of operation because of unusually severe bleeding. This occurred more frequently in older patients (table 15)

TABLE 15.—*Effect of Age on Operative Hemorrhage into Anterior Chamber*

Age, Yr.	No. of Cases	Operative Hemorrhage into Anterior Chamber, per Cent
Less than 60	686	0.9
60 to 69	760	1.6
70 or over	638	2.8

and in patients in whom the sections were deeply placed. No other factors were found to have any relationship to hemorrhages at operation. The hemorrhages occurring at operation were absorbed rapidly and had no effect on the final visual result.

EXPULSIVE HEMORRHAGE

In 18,866 cases of cataract extraction reported in the literature, the incidence of expulsive hemorrhage was 0.3 per cent.[6] Three such

6. de Wecker, cited by Ziegler, L. S.: The Problem of Choroidal Hemorrhage in Cataract Extraction, in Contributions to Ophthalmic Science, Menasha, Wis.

(Footnote continued on next page)

hemorrhages occurred in our series, 1 at the time of operation, another a few hours after operation and the last on the third postoperative day. Although expulsive hemorrhages have been reported to occur in patients as young as 25 years of age, all 3 patients in our series were over 70. Contrary to the general opinion, the blood pressure is usually normal. Of 15 reported cases in which the blood pressure was stated, the systolic pressure was greater than 140 mm. of mercury in only 5, the highest being 180 mm. In only 2 of these was the diastolic pressure above 90 mm. The blood pressures of our 3 patients were 115 systolic and 70 diastolic, 142 systolic and 76 diastolic and 210 systolic and 110 diastolic.

CONCLUSIONS

A statistical analysis is presented of all the cases of hemorrhage occurring in 2,086 extractions of uncomplicated senile cataract. Except for severe diabetes, the general systemic condition of the patient is unrelated to postoperative hemorrhage into the anterior chamber. Operative technics promoting firm closure and avascular healing of the incision reduced the incidence of this complication. These technics include the use of two corneoscleral sutures and a shallow section. The visual results were significantly poorer in the cases with postoperative hemorrhage into the anterior chamber than in the cases without hemorrhage. This was chiefly due to persistent opacities in the vitreous.

Wilmer Ophthalmological Institute.

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EFFECT OF TRAINING METHODS ON COLOR VISION

J. ROSWELL GALLAGHER, M.D.
ANDOVER, MASS.
ELEK J. LUDVIGH, Ph.D.
AND
S. FORREST MARTIN, M.D.
BOSTON
AND
CONSTANCE D. GALLAGHER, B.A.
ANDOVER, MASS.

IN VARIOUS surveys it has been found that from 6 to 8 per cent of unselected males are unable to make the proper responses to a series of color vision test plates.[1] At the present time certain specialized branches of the armed services require that applicants be able to read correctly all the series of these plates; consequently, a number sufficiently large to make color vision testing a matter of considerable significance could be rejected. In a recent publication [1b] the efficiency of some of the plates used in one testing method was questioned, and the suggestion was made that only a small number (ten) of these plates need be used for the satisfactory evaluation of color vision.[2] In that publication [2] these ten plates are referred to as "key" plates. Regardless of the reliability of various testing methods or the desirability of altering present standards, there still remains the problem whether the color vision of those who fail to pass these tests can be modified. Whenever large numbers of persons are excluded either from a branch of the armed services or from a civilian occupation because of a physical disability, there will develop a demand from those affected that the disability be remedied or that the standards applying to it be lowered. In the problem at hand, the rejection of many otherwise well qualified men has led to efforts to

From the Department of Health, Phillips Academy (J. R. Gallagher and C. D. Gallagher); the Howe Laboratory of Ophthalmology, Harvard Medical School, and the Massachusetts Eye and Ear Infirmary (E. J. Ludvigh and S. F. Martin).

1. (*a*) Miles, W. R.: Color Blindness in Eleven Thousand Museum Visitors, Yale J. Biol. & Med. **16**:59-76 (Oct.) 1943. (*b*) Gallagher, J. R.; Gallagher, C. D., and Sloane, A. E.: A Critical Evaluation of Pseudo-Isochromatic Plates and Suggestions for Testing Color Vision, ibid. **15**:79-98 (Oct.) 1942. (*c*) Judd, D. B.: Facts of Color Blindness, J. Optic. Soc. America **33**:294-307 (June) 1943.

2. Gallagher, J. R.; Gallagher, C. D., and Sloane, A. E.: A Brief Method of Testing Color Vision with Pseudo-Isochromatic Plates, Am. J. Ophth. **26**: 178-181 (Feb.) 1943.

improve the color vision of these rejectees so that subsequently they might be able to pass the color vision tests. These efforts have been considered in the light of rehabilitation, inasmuch as it was believed that many applicants failed these tests because of color ignorance, a condition which would obviously be more amenable to treatment than one attributable to a disorder of any physiologic aspect of color perception. However, it is of great importance to know whether such training methods improve the subject's color perception in all situations or whether they only enhance his ability to pass a specific test by improving, at the cerebral level, his ability to interpret that particular test. If the latter is true, the employment of such training methods may be highly undesirable, and the retention of a testing method the results of which can be modified by such procedures would seem questionable. An excellent discussion of the effect of various training methods on visual functions has recently been published by Lancaster.[3] In an effort to determine the effect of training methods, a group of subjects previously identified as being deficient in color vision was studied.

I. TRAINING ON AMERICAN OPTICAL COMPANY PLATES

Method.—All 701 students at a boys' preparatory school were given a color vision test, using 10 of the American Optical Company's Pseudo-Isochromatic Plates.[4] From this group of 701 subjects, 49 (6.9 per cent) were judged to have deficient color vision, an indication that this group was a normal sample. Those whose color vision was deficient were subsequently retested, at which time 46 plates in that pseudoisochromatic series were used. In table 1 the distribution

TABLE 1.—*Distribution of Both Number of "Key" Plates Failed in Initial Test and Number of Plates Failed When the Entire Series of Plates (46) Was Given* *

No. of Subjects	No. of "Key" American Optical Company Plates Failed	No. of Subjects	No. of American Optical Company Plates in Entire Series (46) Failed
2	1	6	8 - 13
2	2	9	18 - 24
6	3	10	25 - 30
3	4	14	31 - 36
8	5	6	36 - 41
7	6	0	42 - 46
8	7		
9	8		

* These 45 subjects, out of the group of 701 who were classified as being deficient in color vision, were later given training; 4 others whose training was not carried to completion are not included in this table.

of the number of key plates and the number of total plates to which the incorrect response was given are recorded. All 49 subjects were selected for the training program. Four were unable satisfactorily to pass the American Optical Company

3. Lancaster, W. B.: Present Status of Eye Exercises for Improvement of Visual Functions, Tr. Am. Acad. Ophth. **48**:413-424 (July-Aug.) 1944.

4. Pseudo-Isochromatic Plates for Testing Color Perception, Southbridge, Mass., American Optical Company, 1940. Gallagher, Gallagher and Sloane.[1b]

color vision test after ten hours of training and are omitted from our data, except for mention in table 2.

Prior to the beginning of instruction, each student's response to each of the American Optical Company Pseudo-Isochromatic Plates and to each of the Ishihara plates[5] was recorded. He was also asked to sort each of a group of colored glass beads into its proper compartment, and the time required and the number of errors made were noted. As a further estimation of color vision the reading on a desaturation test was determined; this test is described in detail later. No subject had further experience with the desaturation test until his training period was completed. At the close of these tests each student was shown the errors he had made in sorting the beads and was urged to study them carefully; he then attempted to correct his mistakes. He was also given sample colored slips from paint advertisement folders and was asked to study these. At every point the subject was urged to exercise care in making decisions, to avoid snap judgments and to refuse to accept the idea that he was handicapped

TABLE 2.—*Data on Four Subjects Not Included in Other Tables Because of Failure Satisfactorily to Pass the American Optical Company Test After Ten Hours of Training* *

Subject	American Optical Company Plates Failed		Ishihara Plates Failed	Beads		Initial Desaturation Test Rating	Hours of Training
	Entire Series	"Key" Plates		Errors	Time		
A. L.†	34	8	14	5	5 min.	12.5	10
D. A.‡	33	8	14	13	2 min. 5 sec.	11	10
R. P.‡	35	8	14	12	5 min.	11.5	10
W. A.§	32	7	14	2	4 min. 3 sec.	11.5	10

* Data on 1 subject (M. D.) are included in our final results despite the fact that his training required more than ten hours.

† The subject made 9 errors on the total series and 2 errors in the key plates of the American Optical Company and 14 errors on the Ishihara plates after ten hours' training, and the rating on the second desaturation test was 12.0.

‡ The subject did not return for a retest after ten hours of training.

§ The subject made no errors on the American Optical Company plates after ten hours' training but was unable to do the test in less than three minutes and thirty seconds and made 6 errors on the Ishihara retest; the final rating on the desaturation test was 11.

or incapable of making color discriminations. When these exercises were mastered, work was begun with color charts, which had been removed from the American Optical Company book of plates, so that random order could be obtained. The subject was instructed first to look for the dots of greatest contrast which vaguely outlined the numbers and then to attempt to trace from dot to dot with a cotton-tipped applicator. Differences in shades were indicated and explained, and continual tracing and retracing of the numbers were practiced. Individual lessons were given two or three times a week. When the subject was apparently able to go through all the test plates accurately and quickly, he was given a formal test on all the 46 plates; and if all were read correctly within a two minute period, he was considered to have passed and put through a final trial on the Ishihara plates and the desaturation test.

A schematic diagram of the desaturation apparatus is shown in figure 1. Two voltage-regulated sources of incandescent illumination, *A* and *B*, are used. The

5. Ishihara, S.: The Series of Plates Designed as Tests of Colour Blindness, ed. 6, Chicago, C. H. Stoelting Company, 1932.

unfiltered light from *B* is focused by a lens and reflected from the semitransparent mirror, *I*, so that at the aperture, *K* (½ inch [1.27 cm.] in diameter), it is somewhat larger than the aperture itself. Light from source *A* passes through filter *E* (Filter, Jena no. RG1, 2 mm., approximating Signal Red) or filter *F* (Filter, Jena no. BG7, 2 mm., approximating Signal Green), whichever it is desired to present. The light then passes through a neutral wedge, *G*, of variable density, compensated, the position of which determines the amount of colored light allowed to pass to the partially transmitting mirror, *I*. This beam of light is also focused

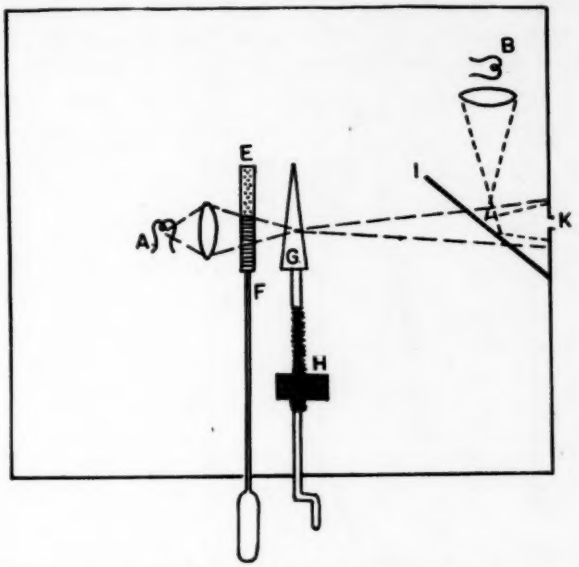


Fig. 1.—A schematic diagram of the desaturation apparatus.

TABLE 3.—*Percentage of Colored Light Which Was Transmitted by the Wedge for Each Successive Desaturation Test Rating Value*

Desaturation Test Rating	Percentage of Colored Light Transmitted
7	1.1
8	1.9
9	3.4
10	6.0
11	10.5
12	18.5
13	25.0
14	57.0

to a circle of the same size as that of the unfiltered light. A piece of "ground cellulose acetate," used as a diffusing screen, is placed over the aperture, *K*. The brightness and apparent angular size of the light are such that foveal vision is used. The neutral wedge, *G*, can be positioned, with considerable accuracy, by means of a screw mechanism, *H*, which permits varying amounts of colored light to be transmitted. At rating 8, for example, the wedge transmitted only about 2 per cent of the colored light, whereas at reading 11 about 10 per cent was transmitted (table 3).

As may be inferred from the diagram and the foregoing description, a white light of constant intensity appears at all times on the diffusing screen. By changing the position of the neutral wedge, different saturations of red and green may be obtained. The test is presented in a darkened room, the subject to be tested being seated 12 feet (3.6 meters) directly in front of the aperture screen. All movements of the operator are concealed from the view of the subject. A high saturation first of red and then of green is exposed in order to show the subject the sort of test with which he is dealing. It is explained to him that at very low saturation he will doubtless be unable accurately to identify the colors but that he must "guess" either red or green, regardless of this. A very low saturation is set up to start with, and red and green exposures are given in

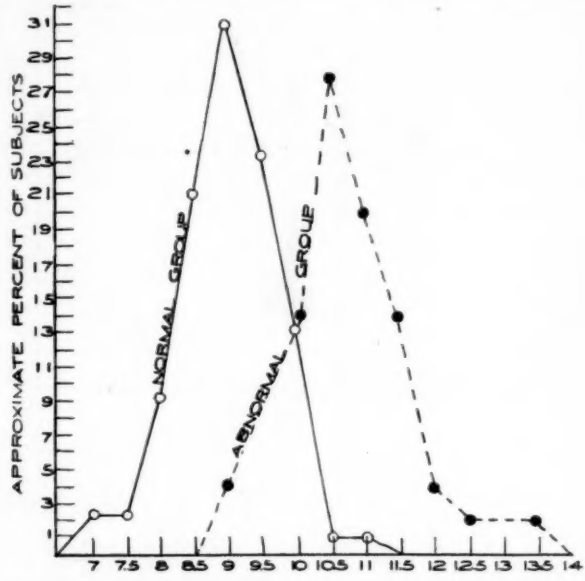


Fig. 2.—The curve of solid lines and circles shows the approximate per cent of the group with normal color vision (111) for each desaturation test rating, and the curve of broken lines and dots gives similar information for the group (49 subjects) whose color vision was abnormal.

random order, previously determined by tossing a coin. As soon as the subject makes an error in identification, a new series of exposures is started at the next higher level of saturation. The position of the neutral wedge when the candidate is first able to identify the colors twenty consecutive times without a mistake is recorded as his rating on this test.

Results.—The normal range of desaturation test ratings of 111 subjects who gave correct responses to the American Optical Company Pseudo-Isochromatic Plates, and who were therefore presumed to have normal color vision, were obtained. Their responses ranged from 7.5 to 11.0, the mean being 9.04 ± 0.04. The reliability of the test ratings can be gaged by analysis of the data obtained on 129 subjects, including 45 persons with abnormal color vision who were tested

and retested. The coefficient of reliability was derived by the Pearson product moment method and is 0.763. The distribution of initial results on the desaturation test on 111 normal and 49 abnormal subjects is

TABLE 4.—*Data Concerning the Forty-Five Subjects Given Color Vision Training*

Name *	American Optical Company Plates Failed		Ishihara Plates Failed		Beads Before Training		Desaturation Test			Number of Training Hours Required
	Entire Series (46)	"Key" Plates (10)	Before Training	After Training	Result	Time	Before Training	After Training	Change †	
R. L.	21	4	13	0	No errors	3′	9	8	+1	2
N. P.	24	5	11	2	No errors	1′ 45″	9	9	0	2
B. V.	19	3	9	4	No errors	2′ 50″	9½	9½	0	2
F. P.	10	3	8	2	No errors	2′	9½	8½	+1	2
J. L.	10	1	9	2	No errors	2′	9½	9	+½	2
C. G.	11	1	11	1	No errors	2′	9½	9½	0	3
R. W.	20	3	10	0	No errors	1′	9½	9½	0	2
W. O.	20	3	9	6	No errors	2′	10	9	+1	2
R. B.	18	6	9	2	No errors	1′ 5″	10	10	0	2
F. B.	12	2	9	0	No errors	2′	10	10	0	1
A. T.	13	3	10	4	No errors	2′ 5″	10	11½	−1½	1
H. R.	31	7	15	1	No errors	2′ 45″	10	10	0	7
G. D.	35	8	15	15	14 errors	4′ 30″	10	11	−1	13
A. M.	29	4	13	0	2 errors	6′	10	11	−1	10
L. K.	31	7	14	9	12 errors	2′ 15″	10½	10½	0	9
S. A.	26	5	11	1	2 errors	1′ 20″	10½	10½	0	3
J. W.	29	5	15	3	No errors	3′	10½	11	−½	5
A. A.	38	6	15	2	No errors	1′ 18″	10½	11½	−1	5
W. W.	20	3	8	0	No errors	3′	10½	9½	+1	4
B. H.	25	4	15	7	2 errors	4′ 15″	10½	10	+½	8
A. C.	36	7	15	7	1 error	4′	10½	11	−½	3
L. B.	31	5	13	2	No errors	1′ 30″	10½	11½	−1	6
G. McL.	36	8	15	4	5 errors	4′	10½	11½	−1	5
E. L.	38	8	14	6	12 errors	1′ 30″	10½	11½	−1	9
D. H.	32	6	14	9	14 errors	2′	10½	10½	0	9
R. M.	35	8	13	6	No errors	2′	10½	10	+½	4
R. P.	33	8	15	2	1 error	2′	11	11½	−½	6
B. M.	29	7	15	7	12 errors	4′	11	10½	+½	9
F. G.	8	2	11	5	No errors	1′ 30″	11	11	0	2
H. P.	23	7	13	3	No errors	2′	11	11	0	1
G. C.	19	5	11	0	No errors	1′ 30″	11	10½	+½	3
A. L.	30	6	15	5	No errors	2′ 15″	11	11	0	4
W. B.	29	6	13	3	3 errors	5′	11	11	0	7
R. McK.	35	8	15	15	14 errors	3′	11	11	0	7
W. A.	37	7	15	5	5 errors	4′ 25″	11½	11	+½	8
A. McL.	27	5	15	4	2 errors	2′ 30″	11½	11	+½	2
C. T.	30	5	15	3	No errors	3′	11½	11½	0	4
A. C.	32	6	14	1	12 errors	3′ 15″	10½	10	+½	10
C. S.	35	8	15	5	25 errors	6′	10½	12½	−2	8
L. V.	28	5	11	1	2 errors	3′	11	11½	−½	3
A. H.	32	7	15	6	2 errors	3′ 45″	11½	10½	+1	7
C. B.	37	8	15	9	12 errors	4′	11½	10½	+1	8
B. H.	34	8	15	2	16 errors	3′	12	10½	+1½	6
R. S.	37	6	15	11	No errors	3′	12	11	+1	10
R. P.	35	7	14	10	25 errors	2′	13½	14	−½	8
Range	8-39	1-8	8-15	0-15	0-25	1′-6′	9.0-13.5	8.0-14.0	−2-+1.5	1-13
Mean and probable error	27.04 ±0.85	5.47 ±0.21	12.80 ±0.24	4.27 ±0.37	4.33 ±0.68	2.96′ ±0.12′	10.59 ±0.08	10.58 ±0.11	+0.01 ±0.07	5.70 ±0.31

* The names are arranged in the order of their rating on the first desaturation test. At the end of the training period all these subjects gave the correct responses to the 46 American Optical Company plates within two minutes.

† An improvement in the desaturation test rating following training is indicated by the plus sign; a decline, by the minus sign.

shown in figure 2. That the American Optical Company test and the desaturation test discriminate in the same fashion between persons whose color vision is weak and those whose color vision is normal is shown

by the correlation 0.82 between the initial American Optical Company test rating and the initial desaturation test rating of the combined group, made up of 111 with normal and 49 subjects with weak color vision.

The number of hours of training required to bring each boy to the point where he could satisfactorily pass the American Optical Company color test is given in table 4, together with the number of key plates and the total number of plates failed before training, the number of Ishihara plates failed before and after training, the number of errors made and the time required for bead sorting before training. Boys quickly learned to complete the sorting of beads; consequently, a record of their performance on this test after training is omitted.

The fact that 45 out of the 49 boys who failed the color vision test were subsequently, after a series of not more than ten training sessions, able satisfactorily to pass this test is of considerable significance. The question at once arises whether these subjects' color perception had undergone a change because of the training methods employed or whether only their ability to interpret the test numbers had changed. It will be noted (table 4) that only 6 of the 45 boys made no errors on the second Ishihara test given at the end of the training period. Training on the American Optical Company plates had improved their ability to interpret the Ishihara plates, but errors were still made by the subjects on this very similar test. The mean number of Ishihara plates failed before training was 12.89 ± 0.24, and, although the number of the American Optical Company plates failed after training had dropped to zero, the mean number of Ishihara plates failed fell only to 4.27 ± 0.37. Before training the correlation between the number of American Optical Company plates failed and the number of Ishihara plates failed was 0.83 ± 0.03 and that between the key American Optical Company plates and the Ishihara plates 0.85 ± 0.03; but after training these correlations were obviously lost.

No significant change in rating on the desaturation test followed the training period. Sixteen boys made some improvement; 16 had the same rating, and 13 had a lower rating, on the desaturation test after training. The mean rating on the desaturation test given subjects with abnormal color vision before training was 10.59 ± 0.08, and the mean of the ratings after training was 10.58 ± 0.11, a difference of only 0.01, whereas the difference between the first tests given to normal and to abnormal subjects was $+ 1.55 \pm 0.09$, giving a critical ratio of 17.22.

Fifteen boys given training which resulted in their ability to pass these tests in December 1943 were retested in May 1944 (table 5). None of these had been given further training in that interval, but 5 passed these tests as part of their examination for various specialized branches of the armed services. On our retest, only 5 made no errors

on the key plates, and only 2 read all 46 plates correctly. All made the same or a poorer response to the desaturation test; only 3 made no errors on the Ishihara test. The effect of training apparently does not persist. These results are comparable to the experience which the armed services have had with men who had been given color vision training: Some failed badly in critical situations which demanded accurate color perception.[6]

II. TRAINING ON DESATURATION TEST

Training on the American Optical Company test plates developed the ability to pass that test but did not result in an increased ability to interpret the colors of the desaturation test. The question arose

TABLE 5.—*Results on Retesting in May 1944 Fifteen Subjects Who Had Successfully Finished a Training Period in December 1943*

Subject	Desaturation Test Rating		American Optical Company Plates Failed Five Mo. After Training		Ishihara Plates Failed	
	Directly After Training	Five Mo. After Training	Entire Series	Key Plates	Directly After Training	Five Mo. After Training
W. B.	11	11	3	1	3	6
C. B.	10½	11½	10	1	9	9
A. C.	10	10½	8	2	1	9
G. G.	9½	9½	1	1	1	2
B. H.	10	10½	2	0	7	4
D. H.	10½	10½	2	0	9	6
J. L.	9	9½	0	0	2	0
R. L.	9	9	5	1	0	2
R. McK.	11	11	13	2	15	13
R. M.	10	10½	11	2	6	8
W. O.	9	10	0	0	6	8
R. S.	11	12	7	1	11	12
F. P.	8½	9½	2	1	2	1
W. W.	9½	10½	1	1	0	0
R. W.	9½	9½	1	0	0	0

whether a period of training on the desaturation test would improve the ability to interpret the American Optical Company test. This investigation seemed particularly desirable because the conditions of the desaturation test are roughly similar to those life situations (i. e., signal lights) in which the aviator, navigator or locomotive engineer has to discriminate correctly, although the varying conditions (while moving at great speed, in fog, etc.) in which these men have to make quick, accurate decisions were not simulated. One who attempts to improve the abnormal color vision of a trainee needs to keep in mind the type of color discriminations which he may subsequently have to make and the conditions under which he may have to make them.

Method.—Six boys, ranging in age from 15 to 17 years, were chosen for training on the basis of their initial performances on the American Optical Company Pseudo-Isochromatic Plates and on the desaturation test. None of those

6. Berens, C., in discussion on Lancaster,[3] p. 422.

selected had failed less than 6 of the key American Optical Company plates; none had a rating of better than 11½ on the desaturation test, and none had any previous training on either the color plates or the desaturation test.

All training was done with the desaturation test device alone. Color plates were used only in the initial and the final testing procedures. At the initial training session the subject was first repeatedly shown the red (and then the green) light at a level of desaturation one step above his previously determined threshold. This was done to increase his confidence and thoroughly to familiarize him with the quality of the lights and the differences between them. When rapid, accurate responses were made at that level, the amount of colored light was decreased by

TABLE 6.—*Data on Six Boys Before and After Training on the Desaturation Test Device* *

Name	No. of Training Periods	Desaturation Test Rating	Steps in Desaturation Test Rating	No. of Plates Failed: American Optical Company "Key" Plates	No. of Plates Failed: American Optical Company Total Series	No. of Plates Failed: Ishihara
A. S.	10					
Before		13	..	6	21	11
After		10½	5	7	23	15
L. L.	7					
Before		12½	..	7	21	13
After		9½	6	7	19	13
M. L.	10					
Before		12	..	6	21	15
After		10	4	6	17	13
G. G.	11					
Before		12	..	8	25	15
After		11½	1	6	15	13
D. P.	9					
Before		12	..	6	16	13
After		10½	3	6	15	13
O. Mc.	11					
Before		11½	..	8	27	15
After		9	5	6	19	15
Average	9.6	....	3.8			
Before		12.1	..	6.8	21.8	13.6
After		10.2	..	6.3	18.0	13.6

* No training on either the American Optical Company test plates or the Ishihara test was given these subjects.

one step and practice was resumed. He was shown the red light (and subsequently the green light) five successive times at that level and urged to pay strict attention to its appearance. The red light was then again shown five times at that level and the green light once; then the green light five times and the red light once. Those procedures were each repeated twice. Next, alternate red and green lights were shown for a total of ten exposures. If after that period of attempting to acquaint him with the two lights he claimed to be ready for a test, he was then given a series of twenty exposures in random order. In the event of incorrect responses, the previous training was repeated; if correct responses were made, the per cent of saturation of the colored light presented was decreased another step. Twenty minute training periods were given four times a week. To avoid the effect of accessory aids to interpretation, the operator was screened from the trainee, and such factors as motion and sound were controlled.

Results.—In table 6 are given the number of training sessions for each boy; his rating on the desaturation test before and after training; the difference, if any, between these two ratings; the total number of American Optical Company plates, and the number of key plates and the number of Ishihara plates failed before and after training on the desaturation test device. It is evident that 5 of the 6 boys made a significant improvement in ability to interpret the red and the green signal light of the desaturation test: The ratings of all but the 1 boy were within the normal range on that test, and 1 (O. M.) achieved a rating equal to the normal mean. It is significant that only 1 boy, after this training, had a rating as good as the mean for normal persons and that the ratings of the others, although within the normal range, fell at the upper end of the normal distribution curve (fig. 2). Further improvement might have been obtained had the training extended over a longer period, but the impression was gained that each subject had reached what seemed to be his maximum capacity: Training was stopped when successive training sessions yielded no improvement. However, despite the definite increase in ability to interpret the desaturation test made by 5 of these 6 boys, none made any significant improvement in performance on the key American Optical Company or the Ishihara plates. Two showed improvement in the total number of American Optical Company plates failed, but even normal persons vary considerably in their responses to many of the plates in that series.[1b] After training on the desaturation test, none failed less than 6 of the key plates; only 2 failed any fewer than they had initially, and yet all but 1 had shown considerable improvement on the desaturation test. It seems clear that although this training method is capable of improving the ability to interpret a signal light of red or green as presented in the desaturation test device, it does not result in a significant increase in ability to interpret the plates of the Ishihara or the American Optical Company color test. It appears that improvement of color vision for all situations cannot be obtained by either of these training methods.

SUMMARY

Forty-nine subjects who had been selected as weak in color vision on the basis of responses to the American Optical Company Pseudo-Isochromatic test plates were subsequently given training on those test plates until all but 4 could satisfactorily pass that particular color vision test. However, although after training perfect responses were made on the American Optical Company test plates by 45 members of this group, only 6 made perfect responses to all the plates in the very similar Ishihara test, and the scores on a color desaturation test, which also had not been practiced, did not improve. A retest on the American Optical Company plates several months later showed a considerable

diminution in ability to make correct responses to these plates and indicated that the effects of this type of training may not long persist.

Six other boys were given the desaturation test, the American Optical Company and the Ishihara color plate tests before and after a period of training on the desaturation device. Five of these subjects showed improvement in their ability to interpret the red and green lights presented by that device after a small number of training periods, but none showed a significant degree of improvement in interpreting the color vision test plates.

Color vision training apparently is successful in enabling most persons with weak color vision to respond correctly to such a test as the American Optical Company plates or the desaturation test herein described, but from this study there is no evidence that either of the training methods used improved the capacity to discriminate between colors in other than the situation in which training was given. Training which enables a person (previously classified as deficient in color vision) to achieve a test rating comparable to that of persons who have normal color vision apparently does not result in the development of the ability to differentiate colors in all situations and under all conditions with the accuracy and speed possessed by those who have normal color vision.

EXPERIMENTAL STUDIES ON THE BLOOD-AQUEOUS BARRIER

FREDERICK W. STOCKER, M.D.
DURHAM, N. C.

II. Electrophotometric Measurements of Fluorescein Content of Aqueous After Intravenous Injection of Fluorescein, the Eye Being Under the Influence of Physostigmine, Pilocarpine, Neostigmine or Atropine [1]

IT HAS been demonstrated by numerous authors, especially by the splendid work of Duke-Elder [2] and Friedenwald [3] and their co-workers, that the penetration of the various constituents of aqueous through the blood-aqueous barrier follows a rather complicated scheme. Electric charge, size of the molecule and possibly other factors influence the ratio of transmission of each constituent. But, on the other hand, it has also been shown that any change of the permeability of the blood-aqueous barrier will affect all constituents to a certain extent, though not equally, whether they are electrolytes, nonelectrolytes or proteins. To mention only two examples, Krause, Yudkin, Stevens, Burmell and Hughson [4] found an increase in the amount of arsenic present in the aqueous after intravenous injection of arsphenamines if the eye had been previously pilocarpinized, and Adler [5] demonstrated a decrease in the permeability of the blood-aqueous barrier to protein in spite of the irritation brought about by the application of ethyl morphine hydrochloride (Dionin) if the eye had been atropinized previously. So far as water is concerned,

From the Department of Surgery, Ophthalmological Division, Duke University School of Medicine.

1. Stocker, F. W.: Experimental Studies on the Blood-Aqueous Barrier: I. New Electrophotometric Method of Measuring the Concentration of Fluorescein in the Aqueous, Arch. Ophth. **36**:612 (Nov.) 1946.

2. Duke-Elder, S., and Davson, H.: The Significance of the Distribution Ratios of Nonelectrolytes Between Plasma and the Intraocular Fluid, Brit. J. Ophth. **27**:432, 1943. Duke-Elder, S.; Quilliam, J. C., and Davson, H.: Some Observations on the Present Position of Our Knowledge of the Intraocular Fluid, ibid. **24**:421, 1940.

3. Friedenwald, J. S.: Dynamic Factors in the Formation and Reabsorption of Aqueous Humor, Brit. J. Ophth. **28**:503, 1944. Friedenwald, J. S., and Stiehler, R. D.: Circulation of the Aqueous: VII. A Mechanism of Secretion of the Intraocular Fluid, Arch. Ophth. **20**:761 (Nov.) 1938.

4. Krause, A. C.; Yudkin, A. M.; Stevens, M. A.; Burmell, W. W., and Hughson, D. T.: The Influence of Drugs on the Transmission of Arsenic into the Aqueous Humor, J. Pharmacol. & Exper. Therap. **39**:153, 1930.

5. Adler, F. H.: The Action of Atropine in Ocular Inflammations, Arch. Ophth. **55**:484 (Sept.) 1926.

the findings of Kinsey, Grant and Cogan [6] seem to demonstrate that a dynamic state prevails in which water of the eye is constantly exchanged for water in the blood and vice versa, the classic conception of inflow of fluid from the ciliary body and iris and outflow through the canal of Schlemn representing only part of the mechanism of exchange. Probably an increase or a decrease in the permeability of the blood-aqueous barrier would also affect the exchange of water. Consequently, if one can demonstrate a change in the permeability using a tracer substance, such as fluorescein, this change may apply at least qualitatively, to all elements involved in the exchange between blood and aqueous. In the past the only disadvantage in using fluorescein has been the lack of a method of accurate measurement of the amount of fluorescein present in the aqueous. This disadvantage, I believe, has been overcome by introducing the electrophotometric method described in the first part of this study.

After the normal curve of transfusion had been established,[1] efforts were directed in the following experiments toward establishing curves showing the change in permeability of the blood-aqueous barrier through the action of the principal miotics and mydriatics by testing the concentration of fluorescein in the aqueous at various intervals after intravenous injection of sodium fluorescein.

EXPERIMENTS

As in the experiments with normal eyes (part I), albino rabbits were used, and 0.25 cc. of a 20 per cent solution of sodium fluorescein per kilogram of body weight was injected intravenously. One drop of one of the following solutions had been instilled previously three times a day for forty-eight hours, the last one being given two hours before the injection of fluorescein: 2 per cent pilocarpine nitrate; 0.5 per cent physostigmine salicylate; 5 per cent neostigmine methylsulfate, and 1 per cent atropine sulfate. At various times after the injection of fluorescein, 0.20 cc. of aqueous was aspirated with a small syringe and a fine, very sharp needle, the cornea having been anesthesized shortly before the puncture with 2 per cent cocaine.

For the benefit of investigators who wish to use this method, I should emphasize the necessity of evacuation of the aqueous with the least possible trauma. If the bulbus is unduly compressed or a blood vessel torn, either at the limbus or in the iris, an excessive amount of fluorescein is found. Readings in such cases are then out of line and must be discarded.

The readings of fluorescein on the photofluorometer obtained with the various specimens of aqueous are recorded in chart 1. The curves represent average readings. It would have been confusing to record all individual readings on the chart, as it contains several curves. Although the readings of course differed somewhat, there was no read-

6. Kinsey, V. E.; Grant, M., and Cogan, D.: Water Movement and the Eye, Arch. Ophth. **27**:242 (Feb.) 1942.

ing below the normal average except for one reading for neostigmine, which was 6 after three minutes.

As previously reported,[1] the readings were most reliable within the ten minute period after injection of fluorescein, after which time they become irregularly increased. This observation, made with animals which were not under the influence of any drug (part I), was confirmed in the present series. Therefore, this "critical" period was exclusively considered. Further investigation will be directed to a study of whether or not any useful information may be obtained from these irregularly increased readings.

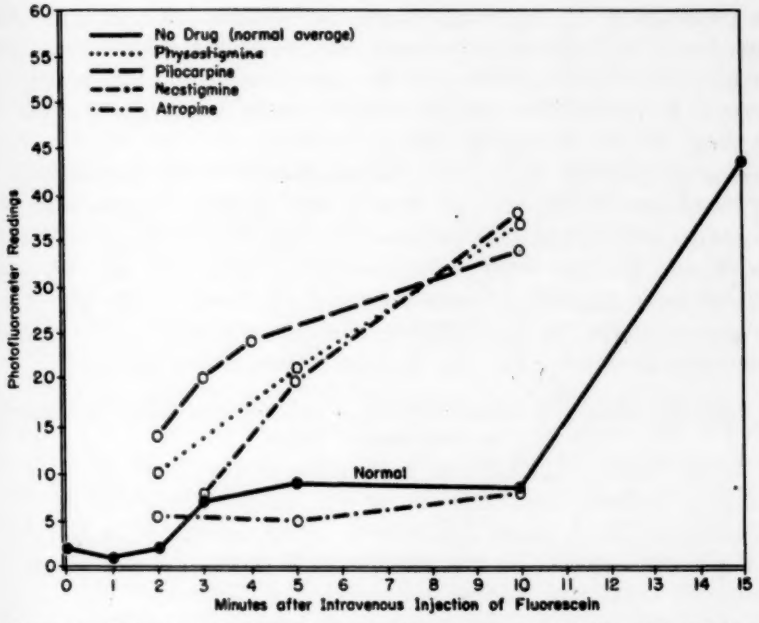


Chart 1.—Influence of physostigmine, pilocarpine, neostigmine and atropine on transfusion of fluorescein into the anterior chamber.

Two main facts are clearly evident: 1. All three drugs known as miotics, physostigmine, pilocarpine and neostigmine, increased the permeability of the blood-aqueous barrier for fluorescein when instilled into the conjunctival sac. 2. Atropine, on the contrary, did not increase the permeability of the blood-aqueous barrier, as all readings were slightly below the normal average.

Seidel [7] already had found that after the instillation of physostigmine and pilocarpine there was an increase of proteins in the aqueous. This, of course, means that the permeability of the capillaries was increased.

7. Seidel, E.: Ueber den Vorgang der physiologischen Kammerwasserabsonderung und seine pharmakologische Beeinflussung, Arch. f. Ophth. **102**:366, 1920.

Swan and Hart,[8] who used inulin and fluorescein, found that physostigmine, carbaminoyl choline chloride and mecholyl (as well as epinephrine in the secondary phase) increased the permeability. However, they did not produce evidence with their method that pilocarpine would increase the permeability, although it increased the total solids in the aqueous. But the latter fact seems to show an increased permeability, at least for certain substances, which was confirmed by my photofluorometric readings.

Atropine in these experiments produced a slight decrease in total solids, an effect which also is consistent with my findings of decreased permeabilty to fluorescein. That Adler [6] had found atropine to decrease the permeability of the blood vessels for proteins has previously been mentioned. It is generally believed that it is not a dilation or a constriction of the blood vessels which is responsible for the increase or decrease in permeability of the capillary walls, but a direct action of the drug on the endothelial cells (Seidel [7]).

The experiments with drugs whose influence on the permeability of the blood-aqueous barrier had already been proved demonstrated that the results with the new method on the whole concurred with previous reports and that the method was reasonably accurate if the necessary precautions in the technic were observed. I therefore thought it was safe to use it for the investigation of substances whose action on the blood-aqueous barrier had not previously been determined.

III. Experiments Concerning Possible Influence of Rutin Given by Mouth on Permeability of Blood-Aqueous Barrier

Rutin ($C_{27}H_{30}O_{16}3H_2O$) is a glucoside derived from flavonol. It was first isolated from tobacco at the Eastern Regional Research Laboratory, United States Department of Agriculture.[9] It was found to be present, however, in a number of other plants and to be especially plentiful in buckwheat, as first discovered by E. Schmuck.[10] Previously, Szent-Györgi and his co-workers [11] had extracted from lemon a substance belonging to the flavonol group for which they gave the formula $C_{28}H_{36\text{-}38}O_{17}$. They demonstrated that the administration of this substance would decrease the permeability of the capillaries for proteins

8. Swan, K. C., and Hart, W. M.: A Comparative Study of the Effects of Mecholyl, Doryl, Eserine, Pilocarpine, Atropine and Epinephrine on the Blood-Aqueous Barrier, Am. J. Ophth. **23**:1311, 1940.

9. Mr. J. F. Couch, senior chemist, in charge of the tobacco section, made the complimentary release of the necessary amount of rutin for this experimental study.

10. Schmuck, E., cited by Couch, J. F.; Naghski, J., and Krewson, C. F.: Buckwheat as a Source of Rutin, Science **103**:197, 1946.

11. Armentano, L.; Bentsáth, A.; Beres, T.; Rusznyák, S., and Szent-Györgi, A.: Ueber den Einfluss von Substanzen der Flavongruppe auf die Permeabilität der Kapillaren: Vitamin P, Deutsche med. Wchnschr. **62**:1325, 1936.

as well as for water. It also prevented hemorrhages in certain cases of purpura. They called it citrin, or vitamin P (P stands for permeability). Because of the close chemical relationship of the two substances, citrin and rutin, the latter was tested clinically by Griffith, Couch and Lindauer [12] and by Griffith and Lindauer [13] and was found to be similarly effective in conditions in which increased capillary fragility was present. In ophthalmology, rutin was reported to be effective in cases of hemorrhagic diabetic retinitis by Hanum.[14]

There is little doubt that the permeability of the blood-aqueous barrier plays an important part in certain cases of glaucoma. It also is known and confirmed by the experiments reported in part II of this study that the drugs generally spoken of as miotics not only contract the pupil but also increase the permeability of the blood-aqueous barrier. On the basis of the work of Küsel,[15] Fortin [16] and others, it is understood that the miotics reduce the tension by pulling the iris out of the chamber angle, thus widening the route of escape to the canal of Schlemn, and possibly by pulling on the scleral spur through the contraction of the ciliary muscle, with the same result. Whether the second type of action of the miotics, the increase of the permeability of the capillary walls, tends to increase or to decrease the tension is not so clearly evident. Clinical experience points to the possibility that either may happen. It is not intended to deal with these clinical facts in this experimental study, but the suggestion may be made that in certain cases the beneficial effect of miosis might be impaired or partially offset by the increased permeability of the blood-aqueous barrier. This explanation could clarify the cases in which miotics have no beneficial effect on the increased intraocular pressure, or have even an adverse one, as in the case mentioned by Luedde,[17] in which physostigmine aggravated the condition. As rutin has been found to tighten the capillary walls, the possibility was to be considered that a combination of rutin and a miotic might improve

12. Griffith, J. Q.; Couch, J. F., and Lindauer, M. A.: Effect of Rutin on Increased Capillary Fragility in Man, Proc. Soc. Exper. Biol. & Med. **55**:228, 1944.

13. Griffith, J. Q., and Lindauer, M. A.: Effect of Chronic Lead Poisoning on Arterial Blood Pressure in Rats, Am. Heart J. **28**:758, 1944.

14. Hanum, S.: Diabetic Retinitis: Clinical Studies of One Hundred and Ninety-Five Cases of Retinal Changes in Diabetics, Acta ophth., 1939, supp. 16, p. 3.

15. Küsel: Ueber die Wirkung des Ziliarmuskels auf das Ligamentum beim Glaucom, Klin. Monatsbl. f. Augenh. **44**:236, 1906.

16. Fortin, E. P.: Schlemm'scher Canal und Ligamentum pectinatum, Arch. de oftal. de Buenos Aires **4**:454, 1929; abstracted, Zentralbl. f. d. ges. Ophth. **22**:419, 1930.

17. Luedde, W. H.: Relation of Capillary and Corneal Osmosis to Glaucoma Therapy, Am. J. Ophth. **23**:388, 1940.

the pressure-reducing action of the latter in those cases in which the increase in permeability of the capillary walls would work to the contrary. Indeed, in a number of cases of glaucoma, I was able to reduce the tension considerably more when I gave the patient rutin by mouth together with a miotic in the eye than when I gave the miotic alone. A report on my clinical investigations carried out in connection with the glaucoma clinic of Duke University School of Medicine and the McPherson Hospital will be published shortly. In the present study I wanted to find out whether an influence on the permeability of the blood-aqueous barrier could be demonstrated in normal rabbits. Since rutin has a vitamin, rather than a pharmacologic, effect, a deficiency should be present in order to demonstrate its action, as most of the vitamins have no or little evident effect on the normal organism. But there was perhaps another possibility of demonstrating the tightening effect of rutin on the capillaries of the blood-aqueous barrier by creating first an increased permeability. In other words, I could increase the permeability by instilling physostigmine, for instance, into the conjunctival sac of an animal which had been treated with rutin by mouth for some time, at the same time instilling the drug into the sac of another animal which had not received rutin. By testing the fluorescein of the aqueous with the photofluorometer after intravenous injection of fluorescein, I should be able to demonstrate whether there was a difference in the amount of fluorescein diffused through the blood-aqueous barrier in the 2 animals.

EXPERIMENTS

Four rabbits receiving the same diet were used. Two of them were given 10 mg. of rutin by mouth twice a day for three weeks. This dose by far exceeds comparatively the usual dose for the adult man, which is 20 mg. three times a day. As rutin is almost insoluble in water, there was no way of administering the accurate doses other than by feeding capsules. Dr. William H. Anderson, intern in the ophthalmologic service, who undertook the feeding, invented an ingenious device by which the rabbits were made to swallow the capsules infallibly.

After three weeks of rutinization 0.25 cc. of a 20 per cent solution of sodium fluorescein per kilogram of body weight was injected intravenously and the aqueous examined with photofluorometer within the ten minute period, as in the previous experiments. After that, the feeding of rutin to 2 of the rabbits was continued for two weeks longer. For the last two days 1 drop of 0.5 per cent physostigmine salicylate was instilled in each eye of the 4 animals three times a day, the last drop being given three hours before fluorescein was again injected in the same way and the aqueous tested with the photofluorometer. The readings are recorded in chart 2.

It may be noted that in the first part of the experiment the readings for fluorescein in the aqueous from the animals that had not received rutin (controls) concurred with the normal curve established previously (parts I and II). The readings for the animals that had been fed rutin were slightly below the readings for the controls at four and five minutes.

One earlier reading, at three minutes, was invalid, as an excessive amount of fluorscein was present, due to too much trauma from a blunt needle. This reading is so much out of line that it should be disregarded. I have recorded it only in order not to become guilty of suppressing any finding.

As to the second part, unfortunately, only 3 correctly collected specimens of aqueous could be obtained. One animal could not be used because an inflammatory reaction, combined with cataract in one eye,

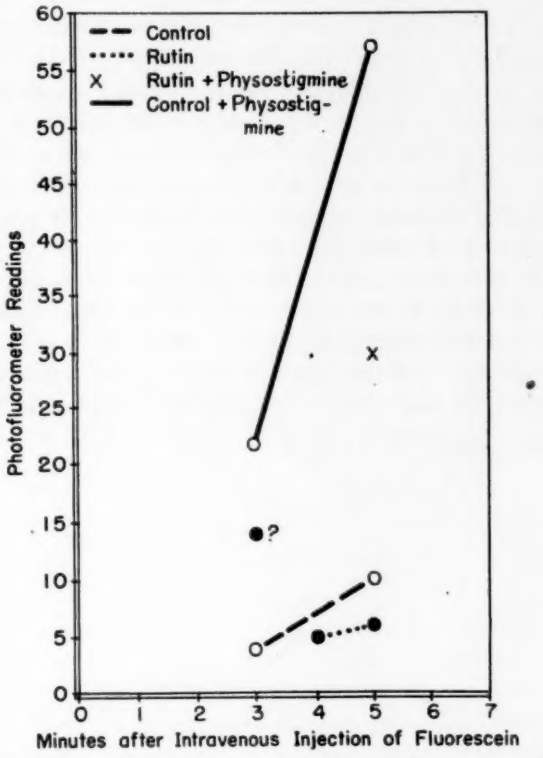


Chart 2.—Influence of physostigmine and rutin alone and combined on transfusion of fluorescein into the anterior chamber.

had set in after the first experiment. So only two readings for physostigmine without rutin and one reading for physostigmine with rutin could be recorded. However, the difference between the two readings at five minutes is so great, that for physostigmine alone being almost twice that for physostigmine with rutin, that attributing a certain significance to it seems justified.

In commenting on these results, I realize that a larger number of readings would be desirable, and I shall endeavor to follow up the

observations with more extensive experiments. As a preliminary report, the following conclusions seem to emerge:

1. No appreciable influence on the permeability of the blood-aqueous barrier can be demonstrated when normal rabbits are fed large doses of rutin for three weeks. If any influence is to be noted, it is in the direction of slight reduction in the permeability. However, the difference between the readings for the controls and those for the rutinized animals is too small to be significant. As mentioned previously, this negative result was expected. Rutin, having a vitamin rather than a pharmacologic effect, would need to meet a state of deficiency or alteration of the capillary walls in order for its influence to be demonstrated.

2. As far as the quantitatively limited present experiments would indicate, rutin given by mouth for several weeks seems to have a considerable tightening effect on the blood-aqueous barrier. The action of physostigmine, which is known to increase the permeability of this barrier after being instilled into the conjunctival sac, is greatly reduced if the animal has been rutinized previously.

Because of the small number of experiments involved, this report on the effect of rutin on the permeability of the blood-aqueous barrier is to be considered as only preliminary. However, in view of the far-reaching possibilities for the medical treatment of glaucoma, further experimental studies and clinical investigations appear to be justified.

1021 Minerva Avenue.

CORNEOSCLERAL SUTURE IN OPERATIONS FOR CATARACT

With Special Reference to the Incidence of Postoperative Hyphemia

OTIS S. LEE Jr., M.D.
IOWA CITY

THE use of sutures for closure of incisions in cataract operations is one of the most useful and valuable refinements in ophthalmic surgery. First described by Williams [1] in 1860, it has become increasingly popular, until at present some type of suture is used in cataract operations in practically every large clinic in this country. Together with the routine use of akinesia and retrobulbar injections, the average ophthalmic surgeon has been able to obtain a greater percentage of successful results in cataract extractions than is otherwise possible.

A review of the literature on this subject shows that most authors are in agreement that sutures (1) promote prompt healing of the wound in most instances; (2) reduce the incidence of prolapse of the iris; (3) reduce postoperative glaucoma by permitting rapid reformation of the anterior chamber; (4) discourage epithelial ingrowth into the anterior chamber; (5) permit rapid closure of the wound, thus minimizing the loss of vitreous should that complication occur during operation; (6) decrease the amount of corneal astigmatism; (7) furnish greater security from postoperative complications in uncooperative patients, and (8) help to prevent cardiac failure and hypostatic pneumonia in aged and weak patients by allowing them greater freedom of movement after operation.

Ophthalmic surgeons do not all agree, however, that sutures aid in reducing the incidence of postoperative hemorrhage into the anterior chamber. Although this complication usually is not a serious one, it may, if severe, increase the number of days of hospitalization. It may also bring about toxic iridocyclitis, secondary glaucoma, staining of the cornea with blood or formation of a pupillary membrane, or it may infiltrate into the vitreous and remain there for an extended period, all of which complications can affect the final visual function or even result in loss of the eye. Older writers were of the opinion that the bleeding came from the iris.[2] More recent investigations,[3] however,

From the Department of Ophthalmology, University Hospitals.

1. Williams, H. W.: Cataract Extractions, Arch. Ophth. **1**:98, 1869.

2. Wheeler, J. M.: A Study of Hemorrhage into the Anterior Chamber Subsequent to Operation for Hard Cataract, Tr. Am. Ophth. Soc. **14**:742, 1916; cited by Philps.[3e]

(Footnotes continued on next page)

point to the incision as the source of hemorrhage. Most hemorrhages occur from the third to the sixth postoperative day. It has been shown [4] that newly formed blood vessels are present in the incision as early as the second to the third day. Any separation of the lips of the wound tears these vessels, resulting in bleeding under the conjunctiva or, more frequently, into the anterior chamber. Many types of sutures have been devised to prevent separation of the wound, with its resulting complications. Among authors claiming success in reducing the incidence of postoperative hyphemia is Stallard,[5] who, using a corneoscleral suture first described by Liégard,[6] did not have a single case of hemorrhage into the anterior chamber in 107 consecutive cataract extractions. Prior to the use of this suture, 30 to 35 per cent of all his patients operated on for cataract in Moorfields had postoperative hyphemia. Philps,[3c] using the same suture, was equally enthusiastic, reporting 120 consecutive cataract operations without hemorrhage. McLean,[7] using a corneoscleroconjunctival suture modified and improved from a corneal suture described by Suarez de Mendoza,[8] claimed an incidence of 3.6 per cent of postoperative hemorrhages into the anterior chamber in 110 cases, as against 10.7 per cent in 64 cases in which only conjunctival sutures were used. Others [9] have reported comparable results in the reduction of postoperative hyphemia when using some type of corneoscleral sutures. On the other hand, Ellett [10] stated that he saw hemorrhages

3. Vail, D.: (*a*) On Hyphema After Cataract Extraction, Tr. Am. Ophth. Soc. **31**:496, 1933; (*b*) On the Mechanism and Cause of Hyphema After Cataract Extraction, Am. J. Ophth. **24**:920, 1941. (*c*) Philps, S.: Post-Cataract Hyphema, Brit. J. Ophth. **24**:122, 1940.

4. Collins, E. T.: Postoperative Complications of Cataract Extraction, Tr. Ophth. Soc. U. Kingdom **34**:18, 1914. Henderson, T.: A Histological Study of the Normal Healing of Wounds After Cataract Extraction, Ophth. Rev. **26**:127, 1907.

5. Stallard, H. B.: A Corneo-Scleral Suture in Cataract Extraction: Its Technic and Advantages, Brit. J. Ophth. **22**:269, 1938.

6. Liégard, H.: Une modification au procede de suture de la cornée dans l'opération de la cataracte, Ann. d'ocul. **149**:119, 1913; cited by McLean.[7]

7. McLean, J. M.: A New Corneo-Scleral Suture, Arch. Ophth. **23**:554 (March) 1940.

8. Suarez de Mendoza, R.: Nouveax faits de suture de la cornée dans l'extraction de la cataracte, Bull. et. mém. Soc. franç. d'opht. **10**:63, 1892; cited by McLean.[7]

9. Leech, V. M., and Sugar, H. S.: Reduction of Postoperative Complications in Cataract Operations with Corneoscleral Sutures, Arch. Ophth. **21**:966 (June) 1939. Kirby, D. B.: Prevention and Handling of Complications Arising During and After Cataract Extractions: Some Practical Points, ibid. **25**:866 (May) 1941. Lehrfeld, L., and Donnelly, E. J.: Corneo-Episcleral Suture in Cataract Extraction, Correspondence, ibid. **24**:401 (Aug.) 1940.

10. Ellett, E. C., in discussion on Peter, L. C.: Sutures in Cataract Extraction, Tr. Am. Ophth. Soc. **45**:46, 1941.

with unpleasant frequency in spite of the use of various types of sutures. Castroviejo, cited by De Voe,[11] using three interrupted corneoscleral sutures, stated his belief that the incidence of hemorrhage in his cases had not decreased with its use. DeVoe,[11] in his statistical survey of 453 consecutive cataract operations, found postoperative hemorrhage into the anterior chamber in about 20 per cent of cases in spite of the use of various types of sutures. He also could detect no difference in the number of hemorrhages with conjunctival and with corneoscleral suture (types not described).

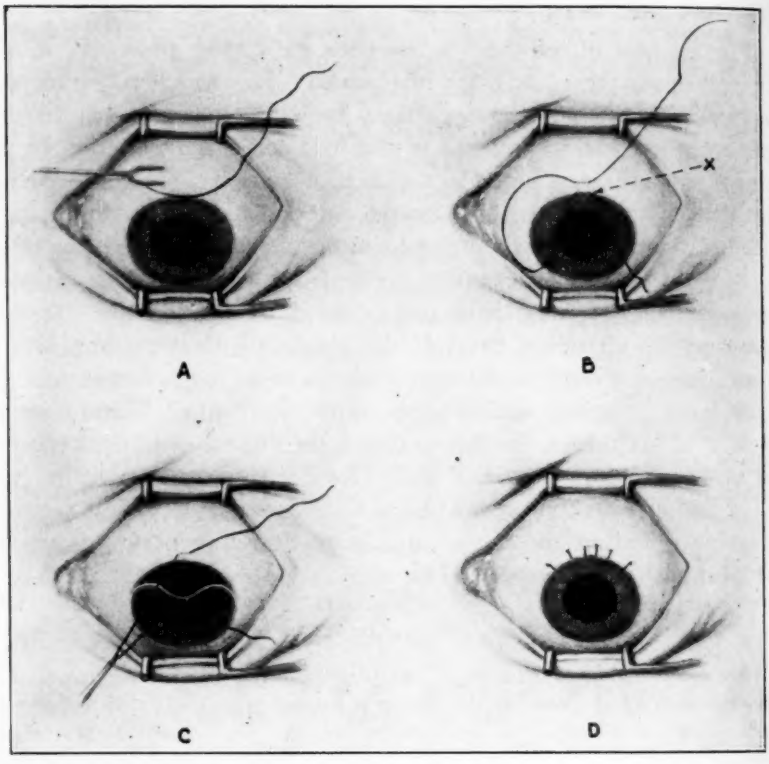
For the past fifteen years it has been the routine procedure in this clinic to employ three or more interrupted limbic-episcleral sutures for the closure of incisions in operations for cataract. The incidence of such complications as prolapse of the iris, delayed reformation of the anterior chamber and secondary glaucoma has certainly been reduced with their use. Hemorrhage into the anterior chamber, however, continued to occur with exasperating frequency. Past studies on the effect on the incidence of postoperative hyphemia of such factors as diabetes, arteriosclerosis, syphilis, hyperpiesis, blood coagulation and bleeding times and the vitamin C level of the blood did not yield any helpful information. DeVoe,[11] in a recent study, came to the same conclusions. In 1945 my associates and I began to use a modified Liégard suture placed at 12 o'clock on the limbus before the incision with the keratome was made, with two additional limbic-episcleral sutures placed on each side of it after extraction of the cataract. The reduction in postoperative hyphemia following the use of this stitch was significant enough to prompt a preliminary report on its use.

TECHNIC

After cocainization of the eyeball, and before the retrobulbar injection of procaine, the 12 o'oclock point on the limbus is marked with the tip of a toothpick dipped in gentian violet. This serves to indicate the point of introduction of the suture, as well as to preserve the landmark of the vertical meridian, since the globe tends to extort or intort after a retrobulbar injection. Fixation of the globe is accomplished by use of a Burch pick. The tip of the pick is placed opposite the point at which the needle is to penetrate the corneal tissue. With a 000000 black twisted surgical silk suture on a three-eighths circle taper or cutting point atraumatic ½ inch (1.27 cm.) needle, the bite is taken in the limbus at 12 o'clock just to one side of the gentian violet mark, the needle entering the corneal tissue sufficiently to insure a firm hold and coming out on the other side of the colored mark. The stitch is usually 1.5 to 2 mm. wide. The thread is pulled through until stopped by a previously prepared double knot, about 3 cm. from the end. The direction of the needle is then reversed, and, with fixation transferred to the

11. DeVoe, G.: Hemorrhage After Cataract Extraction, Arch. Ophth. **28**: 1069 (Dec.) 1942.

opposite side, a bite is taken about 1.5 to 2 mm. above the first one, the needle passing through the conjunctiva and into the scleral tissue and out again. The scleral bite is equal in width to, and lies exactly opposite, the limbic stitch. This is really a mattress suture across the limbus at 12 o'clock. The suture is cut, leaving sufficient length for an adequate loop and a long enough end to permit easy grasp for quick closure of the wound when necessary. The ends and the loop of the suture are then dressed out of the line of incision to permit introduction of the keratome and scissors, without cutting the thread.



A, fixation with the Burch pick and introduction of an atraumatic needle into the limbus; *B*, modified Liégard suture in place (× knot near end of the suture); *C*, lifting of the corneal flap by pulling on the loop end of the suture to facilitate introduction of instruments into the anterior chamber; *D*, modified Liégard suture tied and interrupted limbic-episcleral sutures in place.

RESULTS

A review of the literature shows a wide variation in the incidence of postoperative hyphemia. DeVoe found that it ranged from 1 to 35 per cent, while Philps stated that the number of cases of hemorrhage into the anterior chamber was always higher in the series which were under the direct observation of the authors.

In the present series of 300 cases, dressings were changed twenty-four hours after the operation and daily thereafter. Particular attention was given to the presence of blood in the anterior chamber. Blood in the anterior chamber at the time of the first dressing was not considered the result of postoperative bleeding unless obviously of recent origin. Any sign of increased or new hemorrhage on subsequent dressing was recorded as postoperative hyphemia.

In the first 150 cases (table), three to five interrupted limbic-episcleral sutures were used. In 75 cases of this series a complete iridectomy was performed, whereas in the next 75 cases only a small peripheral iridotomy was done. No significant difference in the number of hemorrhages into the anterior chamber was found between these two series. In contradistinction to DeVoe's results, the type of operation on the iris apparently played no part in the incidence of hemorrhage into the anterior chamber.

Postoperative Hyphemia with Two Types of Sutures

	Interrupted Limbic-Episcleral Suture (150 Cases)				
	No. of Cases of Postoperative Hyphemia				
	Mild	Moderate	Severe	Total	Per Cent
Complete iridectomy (75 cases).....	3	6	2	11	14.6
Peripheral iridotomy (75 cases).....	3	5	4	12	16.0
Total.....	6	11	6	23	15.3

	Modified Liégard Suture (150 Cases)				
	No. of Cases of Postoperative Hyphemia				
	Mild	Moderate	Severe	Total	Per Cent
150 cases with peripheral iridotomy.....	6	3	1	10	6.6
Total.....	6	3	1	10	6.6

In the next series of 150 cases, the modified Liégard stitch was used, in addition to the interrupted corneal-episcleral sutures. All cataracts were extracted through an intact sphincter pupillae, with a small peripheral iridotomy performed in each case. A comparison of the number of cases of postoperative hyphemia in the two series shows an incidence of 15.3 per cent in the first series and 6.6 per cent in the second, a decrease of over 50 per cent in the number of cases of hemorrhage into the anterior chamber in which the modified Liégard suture was used. Moreover, in the first series the bleeding into the anterior chamber was mild in only one fourth of the cases and moderate to severe in the rest, whereas in the second series the hyphemia was slight in over

one-half the cases and moderate to severe in the others. Apparently, even if hemorrhage did take place when the modified Liégard stitch was used, it was more often a small one.

COMMENT

This report is concerned only with a comparison of the efficacy of the interrupted limbic-episcleral sutures and a modified Liégard suture in reducing hemorrhages in the anterior chamber. We have had no experience with the McLean suture,[7] the Verhoeff tract suture[12] or other types of corneoscleral sutures, although these probably offer similar, and perhaps additional, advantages.

Perhaps the reason that use of the interrupted limbic-episcleral sutures is inferior in our hands is that not all of them are truly episcleral but are actually limbic-conjunctival. Those who have had experience with this type of suture know that it is not always possible to get a good bite of episcleral tissue with the needle. This is especially true in the aged. Moreover, an already sectioned globe makes the placing of sutures in the episcleral tissue a more difficult and hazardous procedure, so that occasionally the surgeon, rather than jeopardize the success of the operation, satisfies himself with a limbic-conjunctival suture. We have not infrequently seen sutures hanging loosely from the incision or dropping out altogether on the third to the sixth postoperative day. These probably were only limbic-conjunctival sutures, and not limbic-episcleral as intended. Thus, when strain is put on an incisional wound sutured with such stitches, the support which they should have given is absent. Separation of the lips of the wound, with tearing of the newly formed blood vessels, takes place, resulting in bleeding into the anterior chamber.

With the Liégard type of suture, a good limbic and scleral bite is assured. We have never seen this suture drop off spontaneously. One was inadvertently left in for three months and was still firmly in place when the eye was again seen. The interrupted limbic-episcleral sutures are of secondary importance, as the greatest stress on the limbic wound is in the region of 12 o'clock. Prolapse of the iris is more likely to occur between 11 and 1 o'clock than elsewhere. Frequently the stitch near each end of the incision is deliberately placed in the limbus and conjunctiva, as its main function is to furnish an air-tight wound so that a bubble of air may be injected and retained in the anterior chamber in cataract extractions with a round pupil. This procedure is used to keep the iris diaphragm in place and to prevent the formation of anterior peripheral synechias in the region of the incision.

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12. Verhoeff, F. H.: Corneo-Scleral Suture in Operations for Cataract, Tr. Am. Ophth. Soc. **25**:48, 1927.

Besides its effectiveness in reducing hemorrhages in the anterior chamber, we feel that the modified Liégard suture offers certain advantages.[13] 1. The suture is simple and easy to place, no previous preparation, such as raising a conjunctival flap or making a groove in the limbus, with resultant annoying bleeding, being necessary. 2. The assistant, by pulling on the suture loop on the corneal side opposite the knot, separates the lips of the incision, thus facilitating the introduction of instruments into the anterior chamber by the operator, such as scissors for enlarging the initial keratome incision, iris scissors for iridectomy or iridotomy and capsule forceps for grasping the lens. 3. The wound may be closed quickly by simply pulling on the free end of the suture on the scleral side of the wound. This is of value especially when loss of vitreous is anticipated.

Certain precautions must be kept in mind when this suture is used. 1. The two horizontal bites must be placed as nearly opposite each other as possible to prevent lateral displacement of the two lips of the incision when the suture is tied. 2. The stitch should not be tied too tightly or there may be buckling of the wound. 3. If the keratome is used in making the initial incision in the limbus, the presence of an alert assistant is desirable in keeping the sutures near the scleral bite away from the edges of the blade. Otherwise the stitch may be cut accidentally.

SUMMARY

A modified Liégard corneoepiscleral suture is described. Its use has reduced the incidence of hemorrhage into the anterior chamber in cataract extractions from 15.3 per cent, when interrupted limbic-episcleral sutures alone were used, to only 6.6 per cent, when this suture was added. In addition, when hemorrhages did occur, they were usually less extensive.

The other advantages of this suture are described, and precautions to be taken when using it are given.

13. We feel that the advantage of a prepared conjunctival flap in promoting better healing of the wound, as advocated by some authors, is dependent on the type of incision made, whether corneal or limbic. If it is corneal, the additional nourishment brought by a conjunctival flap to an avascular tissue certainly makes for better healing of the lips of the wound. On the other hand, a limbic incision, as practiced in this clinic, the initial incision being made with the keratome, which is entered about 1.5 mm. behind the limbus, and the section with scissors, usually with inclusion of a narrow tag of conjunctiva, make a prepared conjunctival flap unnecessary.

DANGER OF PENICILLIN THERAPY IN ACTIVE UVEITIS

ELTON R. YASUNA, M.D.
WORCESTER, MASS.

IN A SERIES of papers between 1929 and 1932, Fleming [1] observed that the growth of certain bacteria was inhibited by the chance introduction into the culture plates of the mold Penicillium rubrum, which is abundantly found in rotted fruit, vegetables and stale decaying matter. However, it was not until 1940 that great interest was stimulated in the field by the comprehensive, enthusiastic reports of Florey [2] and Abraham,[3] together with their co-workers. Thereafter experimental and clinical studies appeared in the literature confirming the excellent results obtained with penicillin against certain bacterial infections.

STANDARDIZATION

For clinical application the mold had to be standardized, and two general methods of assay, or standardization, have been developed.

1. *Oxford, or Florey, Unit.*—Florey and Florey [4] employed Staphylococcus aureus plates incubated with Penicillium for twelve to sixteen hours at 37 C. The surrounding zone of bacterial inhibition was observed, and each 24 mm. zone was set up to be equivalent to 1 unit. This was later modified [5] by using Bacillus subtilis, a more stable and sensitive organism than Staph. aureus, and one which gave larger and sharper borders of inhibition on the culture plates.

Read at a meeting of the New York Society for Clinical Ophthalmology.

1. Fleming, A.: On Antibacterial Action of Cultures of Penicillium, with Special Reference to Their Use in Isolation of B. Influenzae, Brit. J. Exper. Path. **10**:226-236 (June) 1929. Fleming, A., and Maclean, I. H.: On Occurrence of Influenza Bacilli in Mouths of Normal People, ibid. **11**:27-134 (April) 1930. Fleming, A.: On Specific Antibacterial Properties of Penicillin and Potassium Tellurite, Incorporating Method of Demonstrating Some Bacterial Antagonisms, J. Path. & Bact. **35**:831-842, 1932.

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3. Abraham, E. P.; Chain, E.; Fletcher, C. M.; Gardner, A. D.; Heatley, N. G.; Jennings, M. A., and Florey, H. W.: Further Observations on Penicillin, Lancet **2**:177-188 (Aug. 16) 1941.

4. Florey, M. E., and Florey, H. W.: General and Local Administration of Penicillin, Lancet **1**:387-397 (March 27) 1943.

5. Foster, J. W., and Woodruff, H. B.: Improvements in Cup Assay for Penicillin, J. Biol. Chem. **148**:723, 1943.

2. *Serial Dilutions.*—In this method the concentration of penicillin required to inhibit the growth of Staph. aureus in agar plates was determined.[6] One unit of penicillin per milligram just inhibited the growth of Staph. aureus in dilutions of 1 : 50,000.

An enzyme, penicillinase, inhibits the action of penicillin, although it probably does not destroy the drug.[7] This enzyme has been extracted from crushed Bacillus coli and other organisms. Susceptible bacteria have been shown to develop a resistance to penicillin after repeated exposure. McKee and Houck[8] produced cultures of pneumococci type III which were resistant to thirty times the greatest amount of penicillin which previously just permitted growth. The mechanism of this induced resistance was not clear, and no penicillin-destroying enzyme could be demonstrated.[9]

Penicillin in vitro is about four times as potent as sulfathiazole against staphylococci and streptococci.[10] Although resembling the sulfonamide drugs in its action, penicillin possesses a number of advantages[11]: 1. Its action is stronger. 2. It is influenced relatively little by the number of bacteria to be inhibited. 3. It is not hydrolyzed by pus. 4. Its toxicity to tissue cells is low. 5. Bacterial resistance is not developed as readily.

Unfortunately, penicillin is destroyed by the hydrochloric acid of the stomach,[12] but if a duodenal tube is used to by-pass the stomach penicillin is absorbed by the intestine without damage to living cells.[13] Rectal administration is unsatisfactory because of the destructive action of penicillinase present in the bowel.[8] At room temperature penicillin solutions retain their potency for about one week.[14]

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6. Rammelkamp, C. H.: Method for Determining Concentration of Penicillin in Body Fluids and Exudates, Proc. Soc. Exper. Biol. & Med. **51**:95-97 (Oct.) 1942.

7. Abraham, E. P., and Chain, E.: Enzyme from Bacteria Able to Destroy Penicillin, Nature, London **146**:837 (Dec. 28) 1940.

8. McKee, C. M., and Houck, G. L.: Induced Penicillin Resistance in a Pneumococcus Type III Culture, Federation Proc. **2**:100 (March) 1943.

9. Rammelkamp, C. H., and Maxon, T.: Resistance of Staphylococcus Aureus to Action of Penicillin, Proc. Soc. Exper. Biol. & Med. **51**:386-389 (Dec.) 1942.

10. Fleming, A., in discussion on Chemotherapy and Wound Infection, Proc. Roy. Soc. Med. **34**:342-347 (April) 1941.

11. Herrell, W. E.: Further Observations on Clinical Use of Penicillin, Proc. Staff Meet., Mayo Clin. **18**:65-76 (March 10) 1943.

12. Rammelkamp, C. H., and Helm, J. D., Jr.: Excretion of Penicillin in Bile, Proc. Soc. Exper. Biol. & Med. **54**:31-34 (Oct.) 1943.

13. Rammelkamp, C. H., and Keefer, C. S., Jr.: Absorption, Excretion, and Distribution of Penicillin, J. Clin. Investigation **22**:425-437 (May) 1943; Penicillin: Its Antibacterial Effect in Whole Blood and Serum for Hemolytic Streptococcus and Staphylococcus Aureus, ibid. **22**:649-657 (Sept.) 1943.

14. Kirby, W. M. M.: Stability of Penicillin Solutions at Room and Incubator Temperatures, J. A. M. A. **125**:628-629 (July 1) 1944.

ABSORPTION AND ADMINISTRATION

Intravenous injection gives an immediate rise in the level of penicillin with a rapid fall, thus necessitating a continuous drip method in order to maintain a high level.[15] No penicillin reaches the cerebrospinal fluid, although some can be detected in the aqueous.[16] Intramuscular administration also causes a rapid rise in the blood level, with the peak remaining for thirty to forty-five minutes, followed by a gradual decline. With this method the concentration in the aqueous is proportional to the dose, but a high level is never obtained, even with massive doses.[17] After paracentesis the level of penicillin in the secondary aqueous approaches that of the blood serum. By this route injections should be given every three hours. Subcutaneous absorption is very slow and somewhat painful. A level of at least 0.156 Florey unit per cubic centimeter of serum is desirable for effectiveness against staphylococci, with lower levels required for streptococci. Oral administration with the use of suitable capsules, such as cellulose acetate phthallate, to withstand the gastric secretions has been developed.

Negligible amounts of penicillin reach the aqueous, vitreous and lens by any of the aforementioned methods of administration, and none is excreted in the tears.[18] Therefore other methods of administration have been employed in ophthalmology.

Topical administration directly to the cornea and conjunctiva gives excellent concentrations on the anterior surface of the globe.[19] Preparations of 300 to 500 units per cubic centimeter in 0.9 per cent solution of sodium chloride are generally employed and should be given frequently, generally about every ten to sixty minutes, depending on the severity of the infection. After constant corneal baths (20,000 units per cubic centimeter) in rabbits, high concentrations have been found in all portions of the eye except the vitreous, the posterior portion of the uvea and the retina.[20] Von Sallmann [18b] has been able to increase the concentrations of penicillin in the cornea, aqueous and iris with the use of iontophoresis.

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15. Struble, G. C., and Bellows, J. G.: Studies on the Distribution of Penicillin in the Eye, J. A. M. A. **125**:685-690 (July 8) 1944.

16. von Sallmann, L., and Meyer, K.: Penetration of Penicillin into the Eye, Arch. Ophth. **31**:1-7 (Jan.) 1944.

17. Town, A. E., and Hunt, M. E.: Concentration of Penicillin in the Aqueous Humor Following Systemic Administration, Am. J. Ophth. **29**:171-175 (Feb.) 1946.

18. (*a*) Bellows, J. G.: Penicillin Therapy in Ocular Infections, Am. J. Ophth. **27**:1206-1219 (Nov.) 1944. (*b*) von Sallmann, L.: Penetration of Penicillin into the Eye: Further Studies, Arch. Ophth. **34**:195-201 (Sept.) 1945.

19. Scobee, R. G.: Penicillin in the Treatment of Perforating Ocular Injuries and in Uveitis, Am. J. Ophth. **28**:380-387 (April) 1945.

20. Herrell, W., and Heilman, D.: Cytotoxic and Antibacterial Activity of Gramicidin and Penicillin: Comparison with Other Germicides, Am. J. M. Sc. **206**: 221-226 (Aug.) 1943.

but even with this method none could be detected in the vitreous or the lens.

Cotton packs saturated with penicillin (500 units per cubic centimeter) and placed in the lower fornix [18b] have proved satisfactory and provide a convenient method for obtaining high levels in the cornea, aqueous, iris and ciliary body. Depletion of penicillin in the ocular tissues usually occurs in about eight hours. Scobee [19] suggested using 1.4 per cent instead of isotonic (0.9 per cent) solution of sodium chloride, since the former is isotonic with the tears. The addition of a wetting agent, such as zephiran chloride, has been found to increase the absorption.[20]

Penicillin can be given subconjunctivally (500 units in 0.5 cc. of isotonic solution of sodium chloride). This method is irritating but places the drug near the site desired. Rycroft [21] advocated using larger doses (4,000 units) to speed diffusion and avoid producing resistance to penicillin. He reported 10 cases in which the aqueous was aspirated fifteen to ninety minutes after the subconjunctival injection and found that bacteriostasis of susceptible organisms in the aqueous was produced within thirty minutes. Penicillin can also be injected directly into the anterior chamber (200 units in 0.25 cc. of solution of sodium chloride).

Local sensitivity to the drug after topical application was seldom experienced and then usually was not severe. Redness, thickening, ptosis and fissures of the lids have been described.[22] Few systemic reactions of a severe nature have been encountered.[23] These untoward reactions have been urticaria, fever, transient azotemia, thrombophlebitis, chills, faintness and muscular cramps, but most of these reactions were thought to be due to the impurities in the preparation rather than to the penicillin itself.

PENICILLIN THERAPY OF OCULAR INFECTIONS

The value of penicillin for ocular infections has not yet been as clearly demonstrated as its usefulness in treatment of many systemic diseases, such as septicemia, meningitis and gonorrhea. At present the place of penicillin in ophthalmic therapeutics appears to be that of aiding, and possibly replacing, the sulfonamide compounds, which are limited in their use. It may be said that the sulfonamide drugs in ophthalmology have not lived up to the high expectations of a few years ago.[24]

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21. Rycroft, B. W.: Subconjunctival Penicillin and Intra-Ocular Infection, Brit. J. Ophth. **29**:501-511 (Oct.) 1945.

22. Vorisek, E. A., and Evans, A. L.: Penicillin Administered Locally in Gonorrheal Ophthalmia: Sensitization Reaction, Am. J. Ophth. **28**:520 (May) 1945.

23. Lyons, C.: Penicillin Therapy of Surgical Infections in the U. S. Army: Report, J. A. M. A. **123**:1007-1018 (Dec. 18) 1943.

24. Chance, B.: A Clinician's Experience with Sulfanilamide, Am. J. Ophth. **23**:900-904 (Aug.) 1940. Heath, P.: Chemotherapy in Ophthalmology, J. A. M. A. **124**:152-155 (Jan. 15) 1944.

Only for those ocular infections in which cultures of penicillin-susceptible organisms have been obtained has the drug shown itself to be of proved value, and this is all that one should expect. Thus, in cases of ophthalmia neonatorum excellent results have been reported with the use of penicillin locally. Sorsby [25] studied a series of 85 cases, and in all instances in which full treatment was given he obtained rapid cures. He advocated local instillation of penicillin (2,500 units per cubic centimeter) every five minutes until the tendency for pus formation was controlled, after which the medication was given hourly.

Penicillin also has been found to be a therapeutic aid in cases of trachoma, again an infection of the external eye. Darius [26] treated both the acute and the chronic form with penicillin topically in a 1:500 dilution and had uniformly good results. In all these conditions good results had also been reported with sulfonamide therapy.

Except in some of the infections of the external eye, cultures of penicillin-sensitive bacteria are rarely obtained. Isolation of an organism is difficult in the case of inflammatory diseases of the cornea, uvea, lens, vitreous, retina, choroid and sclera, which today constitute the more serious ocular conditions encountered. Reports by various authors on the value of penicillin in treating the infectious conditions of the inner eye have not been in agreement.

Excellent results were obtained by Mietus [27] in 3 cases of severe ocular trauma with developing ciliary injection. In each case typhoid vaccine was given intravenously and atropine locally in addition to the penicillin, and in each instance the eye quieted rapidly. In conclusion, he expressed the opinion that "penicillin is a wonderful new therapeutic agent." Cashell [28] also reported a cure in a case of an infected injured eye following the use of penicillin both topically and by injection into the anterior chamber. Subsidence of the inflammatory process in an eye with endophthalmitis and hypopyon of spontaneous origin [29] has also been described, although the final vision was poor. The patient was also given sulfadiazine intravenously, sulfamerazine orally and atropine locally. The authors concluded that the penicillin was of value, but it would appear difficult to judge whether the sulfonamide therapy

25. Sorsby, A.: Penicillin in Ophthalmology: Interim Review, Brit. J. Ophth. **29**:511-536 (Oct.) 1945.

26. Darius, D. J.: Penicillin Treatment of Trachoma: Preliminary Report, Am. J. Ophth. **28**:1007-1009, 1945.

27. Mietus, C. A.: Ocular Therapy with Penicillin Used Topically, Intraocularly, and Systemically, with Case Reports, Am. J. Ophth. **28**:173-179 (Feb.) 1945.

28. Cashell, G.: Treatment of Ocular Infections with Penicillin, Brit. M. J. **1**:420-421 (March 25) 1944.

29. Green, M. I., and Jakobovits, R.: Enophthalmitis Subsiding After Treatment with Penicillin, Am. J. Ophth. **28**:191-193 (Feb.) 1945.

or the penicillin, or perhaps neither, was the important therapeutic factor.

Uveitis.—The most frequent inflammatory process of the inner eye is uveitis. Reports on the treatment of this condition with penicillin have come chiefly from the military services, since penicillin was available earlier in military than in civilian practice. Scobee [19] found that the administration of 150,000 units of penicillin intramuscularly for five to twelve days had a pronounced effect in 75 per cent of his series of cases of nongonococcic uveitis. The number of cases could not be given, for reasons of military security. In his discussion, he stated, however, that "if the patient received nothing but systemic penicillin plus atropine drops, relapses would invariably occur in five to seven days" and that "in no instance was a complete cure effected with penicillin alone." It appears that other therapeutic measures were employed in conjunction with penicillin and that the author questioned whether penicillin would be of benefit if used alone.

A combined comprehensive report from five hospitals of the Army Air Force on the treatment of nonspecific uveitis with penicillin was reviewed and analyzed by Irvine and associates.[30] Fifty-six cases were collected, in all of which the condition was treated similarly with intramuscular injections of penicillin. Only in cases of acute iridocyclitis (16 cases) was significant improvement noted, but even in this group the author felt that "this improvement appeared to be no greater than would be expected with ordinary forms of treatment such as atropine, heat and foreign protein." The remaining 40 cases consisted of 15 cases of chronic iridocyclitis and 25 cases of acute and chronic choroiditis, and in only 2 of these (5 per cent) was there any significant improvement. It was concluded that penicillin was of questionable value in the treatment of uveitis.

At Fort Snelling, Minn., the most frequent cause of hospitalization in the ophthalmologic service was active uveitis. In service, patients with this condition were usually hospitalized, thus allowing the study and treatment of the patient to be as complete as desired. The treatment usually consisted in penicillin intramuscularly, atropine and hot packs locally and typhoid vaccine intravenously. In the 10 cases followed, the results were similar to those found by Irvine and associates,[30] who expressed their belief that penicillin did not influence the course of the disease and that improvement was no greater than with the usual therapeutic procedures.

However, 2 cases of unusual interest raised the question whether the penicillin therapy may actually have been detrimental to the uveitis.

30. Irvine, S. R., and others: The Treatment of Non-Specific Uveitis with Penicillin, Am. J. Ophth. **28**:852-855 (Aug.) 1945.

REPORT OF CASES

CASE 1.—A white man aged 43, single, while awaiting separation from the service, was referred to the hospital because of active iridocyclitis of the right eye of three days' duration. At the age of 21 he had acute urethritis, which was diagnosed as gonorrhea. Since then he has had frequent mild recurrences of the urethral discharge. During the past twenty years he had had at least ten attacks of iritis, occurring in one or the other eye. The patient was certain none of the attacks occurred before the onset of the original urethritis. Except for "arthritis of his back" for the past five years, for which he had never sought medical care, the history was otherwise without significance. He had never received penicillin.

Examination revealed moderate ciliary injection of the right eye, with vision of 20/70. Both new and old keratic precipitates were abundant, and posterior synechias were present. Details of the fundus could not be made out. The left eye was normal except for several old, well formed posterior synechias. Vision was 20/30. Tension was normal in each eye. He was placed under treatment with hot packs and atropine locally.

In the genitourinary service a thick, mucoid urethral discharge was found, which did not reveal organisms on smear or culture. It was believed that this was an old gonorrheal infection with residual chronic prostatitis. On the third day intramuscular injections of penicillin (150,000 units per day) were begun for this condition. All other studies revealed nothing abnormal except for mild hypertrophic arthritis of the lumbar vertebra. Intravenous typhoid therapy (25,000,000 to 45,000,000 organisms) was given every third day, with good systemic reactions. Scopolamine was substituted for atropine on the fifth day because of incomplete dilatation of the pupil. During the first four days improvement was noted, but then the eye became slowly and steadily worse, with reduction of vision to 20/400 and severe congestion and redness of the ciliary region.

The urethral discharge gradually subsided, and penicillin therapy was discontinued on the twelfth day. At this time the cornea was steamy, the iris muddy and the patient miserable. Tension had remained normal throughout. On the fourteenth day, two days after administration of penicillin had been stopped, the first improvement was noted; and during the next seventy-two hours the inflammation rapidly subsided. By the twentieth day, the eye was white; vision was 20/20 — 3, and details of the fundus were clear. No choroiditis was found.

CASE 2.—A white man aged 25, single, was injured in the right eye by a fragment of glass from a broken bottle. Examination one hour later showed two lacerations of the cornea with involvement of 6 mm. of the temporal sclera. A small bead of vitreous was presenting, and vision was limited to light projection. The bead of vitreous was excised; corneal and scleral sutures were placed, and a large conjunctival flap covering was made. Atropine and metaphen ointment were instilled locally.

On the second day intramuscular administration of penicillin was begun (150,000 units per day) as a prophylactic measure. Three days later a mild ciliary injection was noted, and this gradually increased. The conjunctival flap slowly withdrew, and the corneal and scleral sutures were found to be in good position. These were removed on the sixth day. The patient was given intravenous injections of typhoid vaccine every three days, together with atropine and hot applications locally, but the low grade uveitis persisted. The only positive history was an attack of gonorrhea two years before, which cleared rapidly with sulfonamide therapy and had not recurred.

By the sixteenth day the eye was neither better nor worse; vision was limited to counting fingers at 3 feet (120 cm.), and at this time penicillin therapy was discontinued. Within forty-eight hours the patient felt more comfortable and the ciliary injection had begun to subside. On the twentieth day the eye could be readily opened and the uveitis had almost completely disappeared. Vision was 20/70, and fundus details were beginning to be discernible. Three days later he was transferred to another hospital for convalescent care.

COMMENT

Two patients with acute iridocyclitis were treated by the usual methods, with the addition of penicillin intramuscularly. In both the uveitis became progressively worse, and then on cessation of penicillin therapy, while use of typhoid vaccine and atropine was continued, the inflammatory process subsided rapidly. This may well have been coincidental. However, it is also very possible that the mechanism of the action of penicillin and the causative factors of uveitis have an intimate relationship.

PATHOGENESIS OF UVEITIS

The explanation that uveitis was simply the result of bacterial lodgings in the uvea from a focus of infection has not been satisfactory. The great weaknesses in this theory have been (1) little or no evidence of bacteremia in cases of uveitis, (2) a sterile aqueous and (3) no resemblance of the ocular lesions to those produced by staphylococci and streptococci.

As early as 1913 de Schweinitz [31] expressed the belief that bacterial toxins played an important role in the causation of uveitis. Fuchs [32] stated that the poisons, which must have access to the uveal tissue through the blood stream, were not likely to consist of micro-organisms, but more probably were their toxins; and most recent writers on the subject have agreed with this.[33]

Experimentally, ocular sensitivity has been produced in rabbits by using bacterial products from dead streptococci,[34] an organism frequently suspected in the pathogenesis of this condition. Then, on injection of

31. de Schweinitz, G. E.: Pathogenesis of Chronic Uveitis, Excluding the Syphilitic, Tubercular and Sympathetic Varieties, Tr. Internat. Cong. Med., London (Sect. Ophth.) **1**:7, 1913; Brit. M. J. **2**:398 (Aug. 16) 1913.

32. Fuchs, E.: The Pathogenesis of Chronic Uveitis, Excluding the Syphilitic, Tuberculous, and Sympathetic Varieties, Tr. Internat. Cong. Med., London (Sect. Ophth.) **1**:1, 1913.

33. Jackson, E.: Review of Literature of Chronic Uveitis, Am. J. Ophth. **14**: 1203-1209 (Dec.) 1931.

34. Rosenow, E. C., and Nickel, A. C.: Results in Various Diseases from Elimination of Foci of Infection and Use of Vaccines Prepared from Streptococci Having Elective Localizing Power, J. Lab. & Clin. Med. **14**:504-512 (March) 1929. Brown, A. L.: Chronic Uveitis: Bacteriologic and Immunologic Considerations, Arch. Ophth. **12**:730-750 (Nov.) 1934.

these same bacterial products at a remote site a typical uveal inflammation has resulted.[35] Woods [36] injected bacterial vaccines prepared from organisms isolated from the focus of infection, with resulting exacerbation of the ocular inflammation. He suggested that the diseased eye may be hypersensitive to the bacterial products emanating from the primary focus of infection and that this might be the actual explanation of the uveitis.[37]

Irons [38] has shown that the phenomenon of sensitization was involved in recurrent uveitis. He expressed the belief that the exacerbation may well be due to bacterial toxins generated in the focus, which excite a reaction in the uveal tract, already specifically sensitized by the first attack.

ACTION OF PENICILLIN

It is generally agreed that penicillin is not only bacteriostatic but bactericidal.[39] In studies on the staphylococcus with penicillin, actual lysis of the organisms has been demonstrated.[40] Gardner [41] described certain morphologic changes, such as spherical enlargement and elongation of the cells with increased length of chains, in gram-negative organisms after contact with penicillin.

Therefore in a case of active uveitis it can be presumed that products from dead bacteria are diffusing through the blood stream from a focus of infection, which frequently cannot be determined. These bacterial products or toxins, in turn, are causing an inflammatory reaction in the uveal tissue, which has become sensitized to these toxins.

On administration of penicillin systemically, it is known that some lysis occurs in those bacteria susceptible to penicillin, such as staphylococci, streptococci and gonococci, which also are the frequent etiologic agents in uveitis, according to present beliefs. The consequence of use

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35. Zentmayer, W.: The Prostate as a Remote Focus of Infection in Ocular Inflammations, Tr. Sect. Ophth., A. M. A., 1926, p. 216.

36. Woods, A. C.: Allergy and Immunity in Ophthalmology, in Ridley, F., and Sorsby, A.: Modern Trends in Ophthalmology, London, Butterworth & Company, 1940.

37. Woods, A. C.: Allergy and Immunity in Ophthalmology, Monograph 1, Baltimore, John Hopkins Press, 1933.

38. Irons, E. E.: Etiology of Chronic Iritis, Am. J. Ophth. **14**:1228-1236 (Dec.) 1931.

39. Abraham, E. P., and Chain, E.: Purification and Some Physical and Chemical Properties of Penicillin, J. Exper. Path. **23**:103-115 (June) 1942. Herrell.[11] Abraham and others.[3] Dawson, M. H.; Hobby, C. L.; Meyer, K., and Chaffee, E.: Penicillin as a Chemotherapeutic Agent, Ann. Int. Med. **19**:707-717 (Nov.) 1943.

40. Hobby, G. L.; Meyer, K., and Chaffee, E.: Observations on Mechanism of Action in Penicillin, Proc. Soc. Exper. Biol. & Med. **50**:281-285 (June) 1942.

41. Gardner, A. D.: Morphological Effects of Penicillin on Bacteria, Nature, London **146**:837-838 (Dec. 28) 1940.

of penicillin is the release of more bacterial end products into the blood stream. Thus, in a case of active uveitis the use of penicillin may increase the amount of bacterial toxins in the blood stream by the destruction of bacteria in the focus of infection. This only adds new fuel to an already smoldering fire. If penicillin is discontinued, the production of new bacterial end products is stopped or greatly reduced, thereby breaking the vicious cycle inciting the uveitis.

Most cases of uveitis can be brought under control within a few weeks with the use of atropine, hot applications and some form of foreign protein therapy. Since most observers feel that penicillin is not of value in uveitis, it would seem more advisable not to employ the drug, especially when its use may actually be dangerous. It may be true that the foci of infection (they may be multiple) will be controlled or eradicated by the penicillin. If one believes that penicillin might be of value in clearing the suspected foci of infection, then the medication could be employed systemically a few months after the uveitis had subsided. In the meantime the patient should be under observation for an ocular recurrence.

In this report I have only tried to suggest an explanation for the exacerbation in 2 cases of uveitis treated with penicillin. The explanation has attempted to correlate present knowledge of the cause of uveitis with the action of penicillin on bacteria. Further studies certainly are needed on this subject.

CONCLUSIONS

1. Penicillin does not appear to offer any advantages in the treatment of uveitis as compared with previous methods.

2. Penicillin may cause the uveitis to persist longer than would otherwise be expected. Therefore the drug should not be used during the active inflammatory stage.

44 Pearl Street.

RELATIVE DEFICIENCY OF PARASYMPATHOMIMETIC ACTIVITY IN AQUEOUS OF EYES WITH CHRONIC SIMPLE GLAUCOMA

SYLVAN BLOOMFIELD, M.D.*
NEW YORK

THE STUDIES of Loewi, Dale, Cannon and others have firmly established the validity of the concept of the chemical mediation of nerve impulses. It is now generally accepted that the effects of the somatic and parasympathetic nervous systems are produced by the liberation at the nerve endings of acetylcholine. This substance is quickly destroyed by cholinesterase, an enzyme present in the blood and tissue fluids. The effects of postganglionic sympathetic nerve impulses are the result of the liberation at the nerve terminals of epinephrine. The clinical implications of these findings are emphasized by the fact that in at least one disease, namely, myasthenia gravis, the primary dysfunction may be attributed to interference with the mechanism of acetylcholine activity.

The possible relation of these studies to the problem of glaucoma was suggested by several facts. Since the time of Laqueur, who in 1876 demonstrated the therapeutic effect of physostigmine on the elevated pressure of glaucomatous eyes, the administration of miotics has been the mainstay of the medical treatment of primary glaucoma. Pharmacologically, the miotics are parasympathomimetic drugs, and since their actions are similar to those produced by the release of acetylcholine at autonomic nerve endings they are sometimes referred to as cholinergic. They produce their effects either by a direct acetylcholine-like action on the effector cell or by inhibition of cholinesterase, with consequent prolongation of the effect of whatever acetylcholine may be physiologically present.

The classic theory that the hypotensive effect of these drugs on eyes with chronic simple glaucoma is attributable solely to the miosis they produce has been rendered extremely doubtful by more recent observations.[1] That they play a more basic role in the restoration of the normal regulation of ocular tension has been suggested by recent experi-

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* Research Fellow in Ophthalmology.
From the Ophthalmological Service and the Laboratories of the Mount Sinai Hospital.

1. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, vol. 3, p. 3392.

mental studies of Bloomfield and Lambert.[2] These investigations showed that pilocarpine, the most commonly employed of these miotic drugs, exerted a stabilizing effect on the abnormally increased lability of intraocular pressure which was demonstrated to be present in eyes with chronic simple glaucoma. This regulatory effect occurred in a glaucomatous eye with a fixed pupil. In nonglaucomatous eyes the physiologic stability of the ocular tension was not apparently influenced by this drug.

Such observations suggested the hypothesis that some parasympathomimetic substance, such as acetylcholine, might be physiologically present in the normal eye and play a role in the mechanism of regulation of ocular tension. As a corollary, it seemed possible that the abnormal intraocular pressure associated with chronic simple glaucoma might be associated with a deficiency in the activity of such a cholinergic substance. The therapeutic effect of the miotic drugs in chronic simple glaucoma might thus be attributable to their ability to relieve to some degree such a diminution in parasympathomimetic activity in the eye. Schoenberg [3] previously had suggested on theoretic grounds that the administration of miotics in glaucoma might be a form of replacement therapy, similar to the use of insulin in diabetes mellitus.

The purpose of this investigation was to determine experimentally whether a parasympathomimetic substance actually occurred in the nonglaucomatous human eye and to determine its identity if present. A series of eyes with chronic simple glaucoma was also studied to explore the possibility that some deficiency in the normal activity of such a cholinergic substance occurred in that disease. Since the aqueous humor is, in a sense, a perfusion fluid of the eye, and, with proper precautions, is safely obtainable by paracentesis from the living organ, the study of that fluid seemed suited to this purpose. Because of the pharmacologic nature of this investigation and the extreme dilution of the substances which were studied, biologic methods of assay were employed.

In 1930, Velhagen [4] demonstrated that the aqueous humor of certain animals produced a sympathomimetic effect on the isolated frog heart. Engelhart,[5] one year later, instilled physostigmine into the eyes of rabbits to prevent the destruction by cholinesterase of any acetylcholine present and then exposed the eyes to light for parasympathetic stimulation. Under these conditions, he proved by bioassay that acetylcholine was present in the aqueous humor of these animals. In 1938, Pletneva,

2. Bloomfield, S., and Lambert, R. K.: Lability of Ocular Tension, Arch. Ophth. **34**:83 (Aug.) 1945.

3. Schoenberg, M. J.: Am. J. Ophth. **26**:1282, 1943.

4. Velhagen, K.: Arch. f. Augenh. **103**:424, 1930.

5. Engelhart, E.: Arch. f. d. ges. Physiol. **227**:220, 1931.

Raeva and Voronina[6] studied the biologic effect of the aqueous humor of human eyes and found that sympathomimetic activity was present in some and parasympathomimetic activity in others. They could demonstrate no consistent reaction of the aqueous in normal eyes or in any of the eyes with various pathologic conditions which they studied. The last investigators apparently did not use physostigmine in the eye or the standardized application of light according to the Engelhart technic.

METHOD

The plan of this investigation was to determine quantitatively the parasympathomimetic activity of the aqueous humor of human eyes prepared according to the method applied by Engelhart to rabbits. Each eye to be studied was prepared by the instillation of 1 drop of 1 per cent physostigmine salicylate into the conjunctival sac three times at ten minute intervals beginning one and one-half hours before operation. The purpose of administration of this drug was to inhibit the hydrolysis by cholinesterase of any acetylcholine formed. No other eye drops of any sort were used for twenty-four hours preceding the experiment, and no systemic medication was permitted. For one-half hour before the procedure the bright Hammer lamp of the operating room was focused on the subject eye, with winking permitted. In this way reflex stimulation of the parasympathetic nerves to the eye was produced. Anesthesia was obtained by retrobulbar injection of 2 cc. of 4 per cent procaine hydrochloride. Preliminary studies on rabbits had shown that such a procedure did not produce a demonstrable change in the biologic effect of the aqueous humor of the eye. The conjunctival instillation of local anesthetic solutions was avoided, since their passage into the aqueous might influence the results of the bioassay. Approximately 0.1 cc. of primary aqueous humor was obtained from each eye to be studied by paracentesis and aspiration with a hypodermic needle attached to a tuberculin syringe.

The biologic effect of each sample was tested within thirty minutes on the freshly prepared isolated heart of a spring or summer frog (Rana pipiens) according to the perfusion method of Straub.[7] Fresh active hearts were employed, since such organs respond most readily to parasympathomimetic depressor effects. The preparations used in this study were usually found to be sensitive to acetylcholine chloride in dilutions of over 1: 1,000,000,000. Before proceeding with each bioassay, it was necessary to prove the sensitivity of the isolated heart by testing its response to acetylcholine in such high dilutions. To preserve its activity, the aqueous was added without dilution to the Ringer solution in the cannula of the preparation. A kymographic record of the heart beat was made during each experiment. A quantitative estimation of the parasympathomimetic activity of each sample of aqueous humor was derived by comparison of its effect with that of known dilutions of acetylcholine chloride on the same preparation.

In the course of these bioassays of the aqueous, a delayed sympathomimetic augmentation of the heart beat was noted occasionally following the immediate parasympathomimetic depressor effect. Since this study was primarily concerned with cholinergic activity and these assay preparations were not sensitized for the controlled study of adrenergic effects, the latter were not considered at this time but will be the subject of further investigation.

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6. Pletneva, N.; Raeva, N., and Voronina, E.: Vestnik oftal. **13**:462, 1938.

7. Sollmann, T.: Laboratory Guide in Pharmacology, Philadelphia, W. B. Saunders Company, 1917, p. 190.

SUBJECTS

Samples of the aqueous humor of 40 human eyes were examined in this manner. Twenty of these eyes were from 19 persons without a history or signs of glaucoma. Three of these nonglaucomatous patients were, respectively, 23, 34 and 40 years of age, and the ages of the remaining 16 ranged from 50 to 74, with an average of 60 years. In this series of eyes without glaucoma, 4 were normal; 2 had ptyregiums; 8 had senile cataracts of various degrees of maturity, in 1 of which iridectomy had been done preliminary to extraction, and 6 had undergone extracapsular cataract extractions, with secondary discissions in 3 of them. In none of the eyes was any inflammatory reaction present at the time of our paracentesis. Four of these eyes had high degrees of myopia with associated myopic changes of the fundi. Four of the 19 patients in this group had diabetes mellitus, and in 3 of the eyes diabetic retinopathy was noted. Four other patients had advanced hypertension, and an associated retinopathy was seen in 1 eye. One patient had both hypertension and diabetes mellitus, with advanced retinopathy in the eye tested. A clinical impression was obtained of the atrophy of the iris present in each eye; this varied from none, in the more normal eyes, to an advanced degree, in some of the eyes in the aged and diabetic patients. No relationship was found between the results of the bioassay of the aqueous and the presence of systemic disease or the degree of uveal atrophy apparent in each eye.

The other 20 eyes tested were from 16 persons. Each of these patients presented a definite history and evidence of chronic simple glaucoma. The ages of these patients ranged from 44 to 79, with an average of 62 years. Included in this series of eyes were 5 in which the disease was clinically controlled with pilocarpine alone; 5 not treated surgically in which the glaucoma was not controlled with miotics; 3 in which simple iridectomy had been done, with subsequent control of the disease with supplementary use of pilocarpine in 1 eye and failure of control even with miotics in the other 2, and 7 in which the glaucoma was apparently controlled without miotics after treatment with filtering operations, from three months to ten years before. In the last group, that of eyes which had been successfully treated surgically, a trephination had been done on 1 eye; a modified Lagrange operation had been performed on 2 eyes and 4 eyes had benefited from iridencleisis.

In 4 of these 20 eyes recognized chronic simple glaucoma had been present for less than one year, and in 4 other eyes the disease had been known to exist more than ten years. In the entire series, the visual deficiency, cupping of the nerve head and field defects ranged from none to a pronounced degree, and atrophy of the iris was absent in some eyes and advanced in others. In short, every stage of clinically apparent chronic simple glaucoma was represented in this series of eyes. However, no eye was tested during an acute congestive exacerbation of the disease. The ocular tension as tested with fingers before paracentesis was seemingly elevated in some cases and within normal limits in others, without any apparently related effect on the results of the bioassay.

Five of the patients in this glaucomatons group had hypertensive vascular disease. Another had diabetes mellitus. The aqueous humor from the eyes of these patients did not vary in biologic activity from that of the other patients with glaucoma who did not have such systemic diseases.

RESULTS

In the series of 20 eyes without glaucoma the aqueous humor of 17 produced a definite parasympathomimetic depression in amplitude of

the heart beat. In 15 of these 17 eyes the intensity of this effect was found to be approximately equal to that of a similar amount of acetylcholine chloride in a dilution of 1 : 100,000,000. Figure 1 is the record of one such experiment. In the other 2 eyes in which a parasympathomimetic effect was produced the intensity was sufficient to cause diastolic standstill, an effect that could be duplicated by a similar amount of acetylcholine chloride in a dilution of less than 1 : 1,000,000. The 2 samples of aqueous that produced the latter effect were from a normal eye in a patient aged 23 and an eye with a senile cataract in a patient aged 70, respectively.

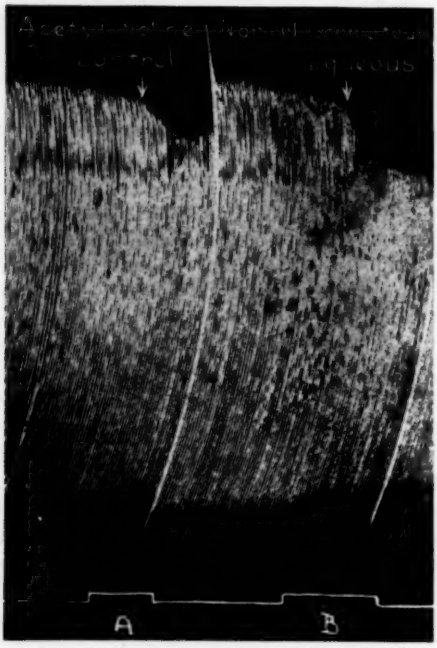

Fig. 1.—Kymographic record of the response of the isolated frog heart preparation to the aqueous humor from a nonglaucomatous eye with senile cataract. *A*, effect of 0.1 cc. of acetylcholine chloride diluted 1 : 100,000,000; *B*, effect of 0.1 cc. of aqueous humor from the nonglaucomatous eye.

In only 3 of the 20 eyes in this nonglaucomatous group did the aqueous humor show no parasympathomimetic activity. On 2 of these eyes extracapsular cataract extraction had been performed with subsequent discission, so that the possibility of contamination of the sample of aqueous with vitreous must be considered. The third eye had a senile cataract. Two of these eyes had a high degree of myopia, and 1 of the patients had diabetes mellitus. Since all these conditions were also present in some of the eyes in the series of 17 the aqueous

of which produced parasympathomimetic effects, their occurrence in these 3 eyes cannot be considered as definitely related to the negative results of the bioassays of their aqueous.

Enough aqueous humor was obtained from 7 of these nonglaucomatous eyes to permit the testing of two samples from each. After one-half the aqueous had been demonstrated to produce depression of the heart beat, 0.1 cc. of a 1 : 10,000 solution of atropine sulfate was added to the contents of the cannula and the second half of the aqueous tested. In each of these 7 samples complete inhibition of the parasympathomimetic

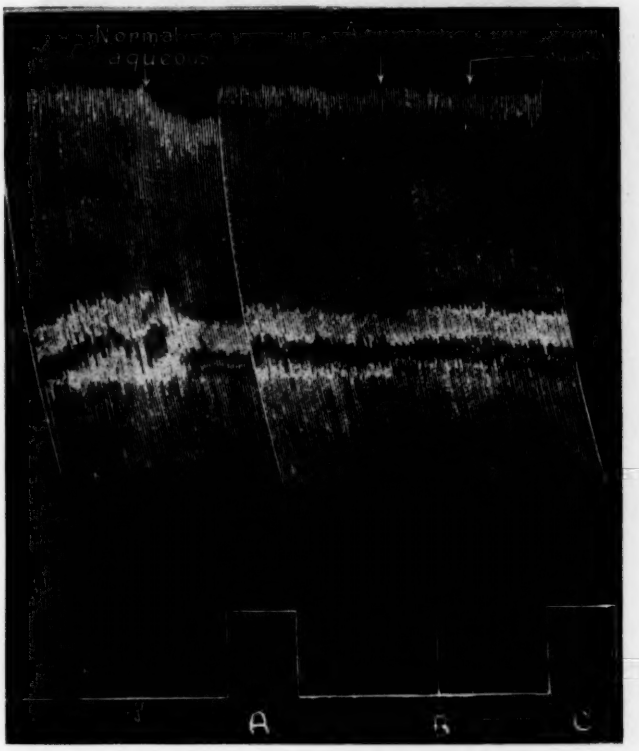

Fig. 2.—Kymographic record showing inhibition by atropine sulfate of the parasympathomimetic effect of aqueous humor from a normal eye. *A*, effect of 0.08 cc. of aqueous humor from a normal eye; *B*, effect of the addition of 0.1 cc. of a 1 : 10,000 solution of atropine sulfate to the perfusion fluid; *C*, subsequent effect of 0.08 cc. of the same sample of aqueous humor as that shown in *A*.

effect previously noted occurred. Figure 2 is the record of one of these experiments. Since it is characteristic of the pharmacologic effect of acetylcholine that it is inhibited by atropine, this demonstration strongly indicates that the parasympathomimetic agent in the aqueous is similar to, or identical with, acetylcholine.[8]

8. Chang, H. C., and Gaddum, J. H.: J. Physiol. **79**:255, 1933.

The samples of aqueous humor obtained from the 20 eyes with chronic simple glaucoma were studied in an identical manner. In 15 samples no parasympathomimetic effect whatever was recorded. Figure 3 is the record of a bioassay of aqueous humor from an eye with chronic simple glaucoma. The aqueous humor of the remaining 5 eyes in this series produced a very slight depression of the heart beat, which on quantitative comparison was found in each case to be less than that produced by an equivalent amount of acetylcholine chloride in a dilution

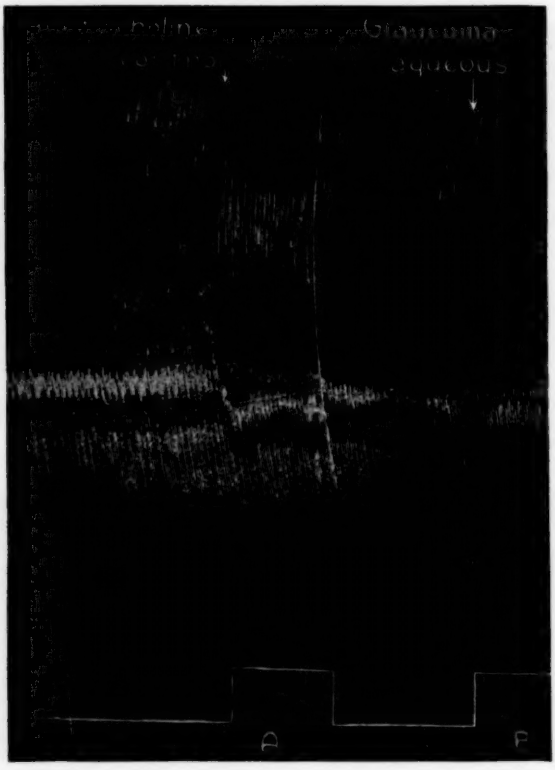

Fig. 3.—Kymographic record of the response of the isolated frog heart preparation to aqueous humor from an eye with uncontrolled chronic simple glaucoma. *A*, effect of 0.1 cc. of acetylcholine chloride diluted 1 : 100,000,000, demonstrating the sensitivity of the preparation; *B*, effect of 0.1 cc. of aqueous humor from an eye with chronic simple glaucoma.

of 1 : 1,000,000,000. These 5 eyes included 2 the tension of which was well controlled with miotics and which showed only minimal impairment of the visual fields and minimal visual defects, 1 in which the tension was controlled with pilocarpine after previous iridectomy but which showed advanced changes in the fields and advanced visual defects, 1 in which the glaucoma was controlled without medication after

iridencleisis and in which only moderate functional impairment had occurred, and 1 not operated on the tension of which was not reduced with miotics and which showed advanced glaucomatous damage. Both eyes of 4 patients with bilateral chronic simple glaucoma were included in this series. In every instance the results of the bioassay were identical in the two eyes of the same subject.

Since parasympathomimetic activity was detectable in the aqueous of only 5 of the 20 eyes in this series, and since even in these eyes it closely

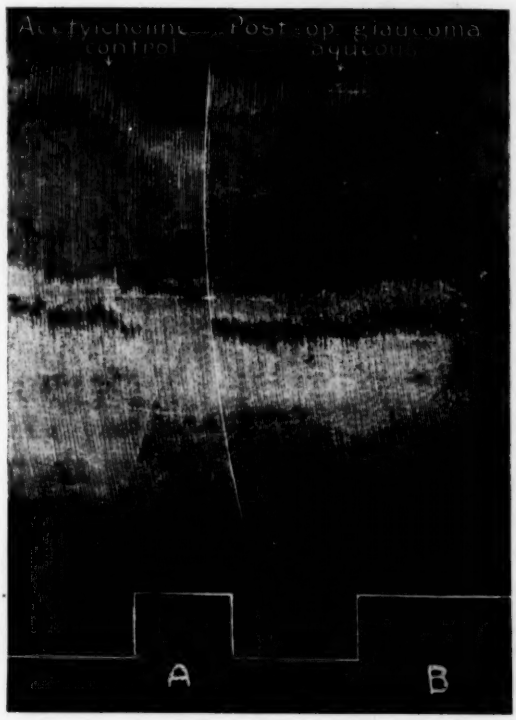

Fig. 4.—Kymographic record of the effect of the aqueous humor from an eye with chronic simple glaucoma which had been successfully controlled by iridencleisis seven months before. *A*, effect of 0.1 cc. of acetylcholine chloride diluted 1 : 100,000,000; *B*, effect of 0.1 cc. of aqueous humor from the eye with chronic simple glaucoma which had been successfully treated by operation.

approximated the limit of sensitivity of our bioassay preparation, no definite conclusions could be drawn with this method concerning a possible relation between the stage of the disease in each glaucomatous eye and the amount of parasympathomimetic activity present in its aqueous humor. It should be noted, moreover, that the absence of biologic effect of the aqueous on these preparations did not necessarily indicate a complete lack of parasympathomimetic activity in that fluid, but showed only that the amount present was too small to be detected

with this method of assay. However, it is apparent that in no instance did the aqueous humor from any of the 20 eyes with chronic simple glaucoma cause a parasympathomimetic effect as intense as that produced by aqueous from 17 of the 20 nonglaucomatous eyes previously described.

As previously noted, in the series of eyes with chronic simple glaucoma 7 were included that had undergone filtering operations some time before, and in each of these eyes surgical intervention had been so successful that the disease was considered clinically controlled without further use of miotics. Nevertheless, the aqueous humor from 6 of these eyes produced no effect on the frog heart, and that of the remaining eye caused only a slight parasympathomimetic effect, equivalent to that of acetylcholine chloride in a concentration of less than 1:1,000,000,000. Figure 4 is the record of the effect of the aqueous from 1 of these eyes which had been successfully operated on for chronic simple glaucoma. In 1 of the 7 cases the opportunity was afforded to test the aqueous before operation, when tension was persistently abnormally high, and, again, three months after successful iridencleisis had reduced the tension to normal. The results of these two bioassays were exactly alike in failing to disclose any parasympathomimetic activity in the aqueous humor. It would appear, therefore, that filtering operations for the alleviation of chronic simple glaucoma, even when successful in clinically controlling that condition, do not affect the deficiency of parasympathomimetic activity of the aqueous humor which is apparently associated with that disease.

COMMENT

The diminution in parasympathomimetic activity of the aqueous humor that has thus been shown to occur in eyes with chronic simple glaucoma may be due either to an actual decrease in the amount of acetylcholine usually present in the aqueous of nonglaucomatous eyes or to inhibition or counteraction of the normal amount of acetylcholine by substances pathologically present. Experiments are now under way to clarify this point.

Since appreciable degrees of cholinergic activity were found present in the aqueous of eyes with a fairly wide variety of nonglaucomatous conditions, and since such cholinergic activity apparently was significantly reduced consistently only in eyes with chronic simple glaucoma, it seems likely that this parasympathomimetic deficiency is related to some physiologic disturbance specific for the latter disease. The question arises whether this reduction in cholinergic activity is an etiologic factor in the development of chronic simple glaucoma or simply the result of the presence of that disease.

It was previously pointed out that the administration of parasympathomimetic drugs has a stabilizing effect on the abnormal lability of

ocular tension that is present in eyes with chronic simple glaucoma. Such drugs also frequently provide therapeutic relief from the abnormally high intraocular pressure present in that disease. These facts strongly suggest that naturally occurring cholinergic substances play a role in the normal regulation of ocular tension. The deficiency of such substances in the aqueous of eyes with chronic simple glaucoma is therefore probably etiologically related to the abnormal intraocular pressure that occurs in that disease. Only in this way can one explain the therapeutic result of administering parasympathomimetic drugs, which in effect relieves that deficiency to some degree.

It is obvious that this demonstration of altered biologic activity in the aqueous humor of eyes with chronic simple glaucoma does not in itself clarify the basic nature of that disease. However, it offers experimental evidence of a physiologic aberration the presence of which was hitherto only suspected, and further investigation of which may throw more light on the problem of regulation of ocular pressure and the therapy of chronic simple glaucoma.

SUMMARY

A method of bioassay is described whereby a quantitative approximation of the parasympathomimetic activity of the aqueous humor of human eyes may be derived.

In 17 of 20 nonglaucomatous eyes with various noninflammatory pathologic conditions, an appreciable parasympathomimetic effect was demonstrable in the aqueous humor.

In each of 7 eyes in which the aqueous humor could be further studied, this cholinergic activity was found to be due to the presence of acetylcholine.

In 15 of 20 eyes in various stages of chronic simple glaucoma, no such parasympathomimetic activity could be demonstrated in the aqueous humor. In the remaining 5 eyes in this series, the intensity of the parasympathomimetic activity present was significantly lower than that which occurred in the aqueous of the 17 nonglaucomatous eyes which produced cholinergic effects.

This relative deficiency of parasympathomimetic activity of the aqueous humor in eyes with chronic simple glaucoma was not altered by the successful treatment of the disease with various filtering operations.

There is evidence that this relative deficiency in parasympathomimetic activity of the aqueous of eyes with chronic simple glaucoma is related to the faulty regulation of intraocular pressure which occurs in that disease.

Miss Mary Carsten gave technical assistance in this work.

1010 Fifth Avenue.

SENSORIAL RETINAL RELATIONSHIP IN CONCOMITANT STRABISMUS

HERMANN M. BURIAN, M.D.
BOSTON

(Concluded from Page 533)

V. ORIGIN OF ANOMALOUS CORRESPONDENCE

Nothing is known about the mechanism which brings about the loosening of the normal sensorial relationship and the revaluation of the spatial values of the retina of the deviated eye. For the time being, one is entirely dependent on speculation in this matter. However, any consideration of the problem must take account of the following facts: (*a*) Anomalous correspondence may be observed even in cases of extreme amblyopia of the deviated eye, and (*b*) it is the prolonged simultaneous stimulation of the fovea of one eye and of an eccentric element of the retina of the other eye that leads in some way to the establishment of anomalous correspondence.

Deeply rooted anomalous correspondence may be observed in cases of extreme amblyopia. For instance, I have seen a student with a congenital, partly absorbed cataract. After this cataract was removed by needling, vision in that eye—in spite of a clear pupillary area and a normal fundus—was never better than 20/200 with correction; most of the time the vision was considerably worse. Nevertheless, and in spite of the fact that he wore no correction for his aphakic eye, the patient when examined one and a half years after the operation for the cataract showed in the double image and after-image tests an anomalous retinal correspondence adapted to his divergent squint of 18 arc degrees.

The teleologic explanation of anomalous correspondence, so often cited in this paper, that it is an attempt of the organism to restore binocular vision on the basis of usage of the eyes, would appear to fall down entirely in the light of this and similar observations. This patient could not have derived any conceivable benefit from the acquisition of a common visual direction between the fovea of the fixating eye and a peripheral element of the retina of the deviated eye. Still less could it have been brought about by a unifying act of attention, as has been stated by some authors (Linksz,[50] Mann [56]), since it is most unlikely that the patient would have paid attention to the extremely faint images

56. Mann, D. S.: Orthoptic Treatment of Anomalous Projection, Brit. J. Ophth. **27**:215, 1943.

received by his left eye. For the same reason, Hering's [57] explanation cannot apply. He expressed the belief that the experience with the relative position of objects in the field of view and their localization relative to the head and body of the patient acquired by frequent alternation eventually leads to the acquisition of different visual directions by the two foveas.

Yet anomalous correspondence adapted to the angle of squint did exist in this patient. One must assume that it came about by a physiologic process which takes place as long as the proper conditions of stimulation are given—a process which again shows the inescapable tendency of the organism to unify the monocular into binocular excitations.

An attempt to explain this physiologic process was made by Sachs.[58] This author assumed that two processes are taking place concurrently. The foveas of a squinting patient receive two different images. The physiologic preponderance of the fixating fovea leads to the neglect of the image received by the fovea of the deviated eye. As a consequence, the physiologic rivalry between the foveas disappears. At the same time, the eccentric retinal element on which the fixation point is imaged becomes increasingly effective in the binocular act; rivalry between it and the fixating fovea develops, and a common visual direction is established. Bielschowsky [31a] did not subscribe to this theory; he maintained that in order to attain rivalry the disparate elements first must have a common visual direction. This is undoubtedly true for normal physiologic rivalry. But could not the rivalry between the fixating fovea and the eccentric retinal element of the deviated eye be of a type different from the normal?

Tschermak-Seysenegg,[30] Bielschowsky,[31a] Braun,[24] Harms [59] and, particularly, Travers [21] made interesting and pertinent experiments concerned with suppression and functional scotomas associated with strabismus which reveal a relationship between amblyopia, suppression and anomalous correspondence. According to Travers' observations, there can always be mapped out by perimetric methods in the deviated eye a region of suppression corresponding on the Bjerrum screen to the retinal area which has a common visual direction with the fovea of the fixating eye. Thus, in cases of normal retinal correspondence this area on the screen has as its approximate center the line of direction of the fovea of the deviated eye; in cases of anomalous retinal correspondence this center

57. Hering, E.: Ueber die anomale Lokalisation der Netzhautbilder bei Strabismus alternans, Deutsches Arch.f.klin. Med. **64**:17, 1899.

58. Sachs, M.: Ueber das Alternieren der Schielenden, Arch. f. Ophth. **48**: 443, 1899.

59. Harms, H.: Ort und Wesen der Bildhemmung bei Schielenden, Arch. f. Ophth. **138**:148, 1938.

is represented by the line of direction pertaining to the eccentric retinal element of the deviated eye which has a common visual direction with the fovea of the fixating eye.

Both Harms and Travers agreed that this regional suppression is intimately associated with anomalous correspondence. Harms went so far as to claim that to establish the presence of regional suppression is equivalent to demonstrating that there is anomalous correspondence.

Travers maintained that the larger the angle of anomaly, the greater is the area of suppression. He formulated the following theory of the origin of anomalous correspondence [60]: In the nonfixating eye, first the macular area is suppressed to avoid diplopia; then the eccentric area on which the fixation point is imaged is suppressed to avoid confusion (simultaneous perception of different object points in the same visual direction). This suppression causes the object point which is imaged on the macula of the deviated eye to be perceived in the monocular visual direction of the fixating eye, and this gradually alters the power of discriminating direction in the deviated component of the binocular visual field. By a succession of processes of suppression and readjustment of the visual directions there finally are established a definite area of suppression and an anomalous correspondence adapted to the angle of squint.

This theory sounds plausible, but it is not borne out by clinical experience. I have never observed gradual changes in the angle of anomaly.[61] Nevertheless, although future investigations must determine the mechanism by which anomalous correspondence is established, these will probably have to be conducted along the lines which were first suggested by Sachs forty-five years ago, and along which Travers and Harms have lately worked.[62]

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60. Travers, T. à B.: The Origin of Abnormal Retinal Correspondence, Brit. J. Ophth. **24**:58, 1940.

61. E. E. Cass (Anomalous Retinal Correspondence, Tr. Ophth. Soc. U. Kingdom **58**:276, 1938) stated explicitly, however, that "it is curious to note during squint training that the false point moves nearer and nearer the macula as macular-binocular vision improves."

62. Travers' findings [21] are as yet by no means fully explained. Most of them do not directly relate to the topic of this paper and will therefore not be discussed here. I wish only to point out that Travers concluded from his results that anomalous retinal correspondence cannot lead to a useful, though inferior, type of binocular vision, as is often assumed. This is, in his opinion, precluded by the regional suppression in anomalous retinal correspondence. Travers' conclusion can at best relate to the cooperation between the macula of the fixating eye and the eccentric element of the deviated eye. There is, however, as a rule little suppression in the other regions of the binocular field (Harms [59] and others), and I [12] was able to show that there may be a high degree of binocular cooperation with anomalous correspondence in peripheral retinal areas when the central area of one eye is suppressed. A case of this type is also reported in the present

The findings of the modern school of psychophysiology of vision will also have to be considered, and its observations and methods may possibly help to furnish a clue to the solution of the problem. A further development of Lorente de Nó's speculations [39] about the point to point relationship of the retinas may be helpful, and it must be kept in mind that Tschermak-Seysenegg, Braun and other representatives of the nativistic school stated the belief that a certain deficiency in the *Anlage* of the normal correspondence is necessary for anomalous correspondence to come about.

VI. CRITICAL REVIEW OF THE LITERATURE OF THE LAST TWO DECADES CONCERNED WITH ANOMALOUS CORRESPONDENCE

As was pointed out by Wheeler,[63] two periods in the literature on anomalous correspondence may be distinguished. The first period, extending roughly to 1925, began about 1895, although occasional attention had been given to the subject prior to that date. This is the period in which the most important fundamental papers appeared, written or inspired largely by physiologists.

During this first period the rank and file of the ophthalmologists did not even suspect the existence of anomalous correspondence. Not until it was recognized by the ophthalmologists at large that strabismus is a sensory as well as a motor disturbance and until interest in orthoptic treatment became more widespread was the subject taken up again. For the past twenty years a rather voluminous literature on anomalous correspondence has sprung up, although, strangely, some of the most recent and most widespread monographs on strabismus do not even mention it.

The present section is concerned with a critical survey of the literature of the second period. Completeness is attempted, but not all papers in which anomalous correspondence is merely mentioned are cited. Only the more important papers are discussed in some detail. A number of papers which have been referred to in previous sections will not be discussed again.

A great deal of confusion reigns in the literature of the last twenty years on anomalous correspondence. It can be traced almost invariably to a lack of knowledge of the literature of the first period and to a lack of understanding of the basic physiologic processes involved. It will

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paper (case 22). Tschermak-Seysenegg [30] discussed in detail the binocular visual act in anomalous correspondence. He stated that there is no doubt that the possibility of binocular mixture and binocular contrast exists in spite of the sensorial inequality of the two eyes. Both eyes participate in the binocular visual field even in anomalous correspondence, though there is to some extent a suppression of the visual impressions of the squinting eye.

63. Wheeler, M. C.: History of Orthoptics, Am. J. Ophth. **25**:569, 1942.

become apparent in the course of the discussion that two main misconceptions are at the root of the confusion: The old projection theory, though in general abandoned in its original form, still prevails in the minds of most authors, and no difference is made between absolute, or egocentric, spatial localization and relative localization, to the latter of which the concept of anomalous correspondence exclusively refers.

This survey will be divided into three parts. The first deals with the theory of anomalous correspondence; the second, with monocular diplopia and binocular triplopia, and the third, with anomalous correspondence as it relates to orthoptic treatment.

I. THEORY OF ANOMALOUS CORRESPONDENCE

In 1931 and 1932 there were published posthumously two articles by Duane [64] which elaborate the contents of an earlier paper by the same author.[65] These papers give a clear presentation of the projection theory as modified by Duane and are helpful in explaining much that has been written subsequently on anomalous correspondence.

According to Duane, the visual impressions are projected or referred to a definite portion of space outside the body, in monocular as well as in binocular vision. In binocular, as in monocular, projection visual and postural elements aid in the localization. The visual element helps one localize an object through the impression produced by the retinal image. In this respect binocular is like monocular projection, except for the added sensation of depth when the retinal images are not quite identical.

Duane stated that the postural elements are the sensations derived from the movements of the head, the conjugate movements of the eyes and, in binocular vision, the sensations derived from convergence. The sensations coming from the muscles of the head tell one whether the face is directed straight forward or not. The eyes are made aware of their movements by the muscle sense. It is this awareness which produces spatial localization. The lateral and vertical conjugate movements of the eyes inform one as to whether the visual plane is horizontal or tilted and whether the object of fixation is straight ahead, to the right or left, or above or below. The sensations arising from the convergence effort determine whether one object appears nearer or farther away than another.

There is, however, an essential difference between monocular and binocular projection. In the former, each eye projects as if it were in its own place, and in the latter, as if each eye were transferred to the

64. Duane, A.: (*a*) Binocular Vision and Projection, Arch. Ophth. **5**:734 (May) 1931; (*b*) Diplopia and Other Disorders of Binocular Projection, ibid. **7**:187 (Feb.) 1932.

65. Duane, A.: Projection and Double Vision: Some New Viewpoints, Arch. Ophth. **54**:233 (May) 1925.

midline. In monocular vision each eye projects with reference to its own axis, and in binocular vision, with reference to the midline, or "bivisual line"; i. e., binocular projection may be conceived as performed by a single cyclopean eye, or *binoculus*. This change in the line of reference is proved by the fact that in physiologic diplopia the double images are projected not to the plane of the fixation point but to the plane in which the object lies which is seen double.

Duane thus showed that the old projection theory is unable to explain physiologic diplopia—which is one of the reasons that Javal and Hering, who were not mentioned by Duane, rejected the projection theory—and accepted the concept of the cyclopean eye. However, he still adhered to the projection theory. Since it does not in itself explain binocular spatial localization, the concept of the "muscle sense" of the eye, introduced by Nagel, the founder of the projection theory, is used to explain both egocentric (at a distance from, or above or below, or to the right or left of, the observer) and relative localization, which are not distinguished.

Duane claimed further that convergence and conjugate movements produce sensations which cooperate in binocular projection and explain physiologic diplopia. This is also supposed to explain pathologic diplopia. In esophoria, for instance, both eyes tend to converge on a point nearer than the fixation point. This excess of convergence is compensated for by an impulse for lateroversion of one eye, accompanied with a conjugate movement of the other eye. Thus, the convergence is reduced in one eye until the eye comes to be directed to the fixation point, while the other eye converges even more than before. Since the two eyes are subject to an equal convergence effort in the case of an ocular deviation, just as in the case of binocular fixation, all images formed on the retina of either eye are projected as though the two eyes were united in the binoculus and their visual axes coincided with the bivisual axis. Diplopia produced by prisms or by paralyses of the ocular muscles are explained analogously.

Before giving Duane's views on anomalous correspondence, a significant paragraph, entitled "Diplopia Always Due to False Projection," [64b] will be reproduced in its entirety:

> It must be noted that binocular diplopia, whether physiologic or pathologic, is always the result of false projection. In monocular vision the eye almost invariably projects correctly; the combination of visual and postural impressions enables it to do this. In binocular vision the two eyes, if acting in a normal way, project correctly the object looked at with even more accuracy than in monocular vision. They also project correctly a few outlying objects, which form images on corresponding points, or which at any rate occupy the horopter. But all other objects are projected out of their true place, and the same is true of all objects seen by the deviating eye. The false projection in both cases is due to the preponderance of the postural expressions derived from convergence over those derived from conjugate movements; i. e., it is due to the fact that when one looks

with both eyes one locates objects with reference to the midline instead of with reference to the visual axes of the eyes themselves.

If the postural impulses derived from conjugate movement chance to reassert themselves and partially or wholly to replace those derived from convergence, the diplopia diminishes (becomes incongruous) or disappears (suppression).

The last sentence contains the essence of Duane's concept of anomalous correspondence. The interplay between the monocular type of vision (projection by conjugate impulses) and the binocular type (projection by convergence impulses) explains "incongruous diplopia" (which exists when the deviation found by the objective tests differs in amount from that shown by subjective tests) and "suppression" (which is the terminal stage of incongruous diplopia and is often associated with it). In ordinary diplopia the deviating eye, dominated by convergence impressions, locates its visual axis in the midline. When the deviated eye is wholly under the influence of conjugate impressions, it locates its visual axis where it actually is; but since the image of the fixation point is less distinct it will be suppressed. If the reversion to the monocular type of vision is not complete, the eye, being under the influence of both convergence and conjugate impulses, locates its visual axis along some intermediate line.

In discussing Duane's theory of spatial localization, it must be said that with the introduction of the cyclopean eye the projection theory is no longer applicable and becomes devoid of meaning.[14] The introduction of the "muscle sense" does not give it meaning since it has long since been established that there is neither anatomic [66] nor physiologic evidence (von Helmholtz,[11] Hering,[9c] Hofmann,[11] Tscherning,[67] Irvine and Ludvigh [68]) for a muscle sense of the eyes of such a highly differentiated nature that it could account for all visual spatial orientation. The theory breaks down completely when it is applied to the explanation of anomalous correspondence after successful operation on the ocular muscles which has restored the balance of the conjugate movements. The paradoxic diplopia which is so often, and often so persistently, observed cannot be accounted for on the basis of the "muscle sense."

Only the theory of retinal correspondence on the basis of common subjective visual directions offers an unequivocal explanation for all phenomena observable in normal binocular vision and in pathologic cases.

Duane's theory may be considered obsolete, and I would not have given it such detailed presentation if it were not for the fact that similar

66. Irvine, S. R.: Histology of Extra-Ocular Muscles, Arch. Ophth. **15**:847 (May) 1936.

67. Tscherning, M.: Physiologic Optics, translated by C. Weiland, Philadelphia, Keystone Publishing Company, 1900.

68. Irvine, S. R., and Ludvigh, E. J.: Is Ocular Proprioceptive Sense Concerned in Vision? Arch. Ophth. **15**:1037 (June) 1936.

views, which are the source of much confusion,[69] still crop up in the orthoptic literature on the subject of anomalous correspondence.

This is evident also in a paper by Verhoeff,[10] in which he wished to correct what he believed to be prevalent misconceptions concerning certain visual phenomena associated with strabismus, particularly as regards anomalous retinal correspondence, or, as he termed it, anomalous projection.

It is difficult even for one well versed in the subject to follow Verhoeff's paper. For one not intimately acquainted with the subject it is probably impossible to understand it. Yet Verhoeff came to such sweeping conclusions regarding anomalous correspondence that his paper commands close attention.

Verhoeff began his paper by defining corresponding retinal points and stated that many definitions have been attempted, some of which are evidently inaccurate while others are inadequate or ambiguous. I do not know what authorities Verhoeff consulted about this definition, or where he found the two definitions which he quoted as examples, since he gave no references. But surely they were not given by the best authors.

According to the first definition, "corresponding retinal points are retinal points which are projected to the same place in space." This definition is certainly erroneous. It is erroneous, first, because "retinal points" cannot be projected into space, but only visual impressions; second, because visual impressions are not projected into (objective) space but are localized in (subjective) visual space, and, third, because visual impressions produced by simultaneous stimulation of corresponding retinal elements do not of necessity have to be localized at the same place in subjective space. Verhoeff objected to this definition because it "does not include the case in which an image on one retina is projected 6 inches (15 cm.) away and an image in the corresponding area is projected 6 miles (9,656 meters) away." This objection is not valid, since the concept of retinal correspondence does not imply depth localization, but pertains only to the relative localization in the horizontal and vertical

69. To cite one example, Hoorens[45] stated: "The majority of the classic writers give no plausible explanation of false projection. I believe that I can explain the majority of cases in the following way: False projection is found mostly in patients with alternating strabismus. The alternating strabismus continues after the operation and is so rapid that the patient thinks he can see two lights at the same time. But since after the operation the internal rectus muscle has to exert less effort to straighten the eye than before the operation, the patient experiences the sensation that the object seen by the strabismic eye is located more to the nasal side. He therefore projects it more to the nasal side, i. e., sees it in crossed diplopia."

As another example, see Pascal, J. I.: Visual and Orthoptic Training, Am. J. Ophth. **17**:801, 1934.

dimensions. The distance at which stimuli are localized cannot enter into the definition of retinal correspondence, but only the direction in which they are seen is concerned.

The second definition quoted by Verhoeff, "that corresponding retinal points are retinal points that are projected in the same direction," comes, therefore, closer to the truth, although, again, neither "retinal points" nor, for that matter, visual impressions are "projected" in any direction. Verhoeff stated that this definition does not distinguish between "normal and anomalous projection," which he endeavored to prove in his paper.

Verhoeff then gave his own definition of corresponding retinal points. Using in schematic and slightly modified form the old experiment of Hering by which he proved the existence of common visual directions, Verhoeff introduced a new terminology. The line connecting the center of an object point with its image on the retina he called a "visual axis." He then stated—without proving it in the text or in the diagram—that objects lying on certain "visual axes" of the two eyes are seen to lie on an imaginary line, which he termed a "binocular visual axis." Corresponding retinal points were defined as the retinal optical terminals of corresponding visual axes.

An analysis of this definition shows that it is by no means really new, but its formulation is such that it confuses, rather than clarifies, the concept of corresponding points. What Verhoeff termed the "visual axis" is nothing other than what is known as the "line of direction." This line is simply a geometric construction which determines which retinal element will be stimulated. By no stretch of imagination is it possible to conceive that any two "corresponding visual axes" could coincide or appear to coincide—not even "as visualized from their respective eye." Not even the strictest adherents of the projection theory have ever claimed that the lines of direction coincide; they have only claimed that the visual impressions are projected outward along the lines of direction (i. e., Verhoeff's visual axes).

How and why these visual axes coincide, Verhoeff did not say. But the gap is easily filled if the concept of the subjective visual directions, which Verhoeff did not recognize, is introduced. His definition, then, in essence, becomes identical with the classic one, according to which corresponding retinal elements are those elements which have a common subjective visual direction.

What has been pointed out here is, to my mind, not a play on words; it goes to the essence of the binocular visual process. A clear understanding of these processes requires a clear terminology, and, vice versa, a clear terminology makes for clear understanding. This has been emphasized time and again by Lancaster.[6]

The main point which Verhoeff made in his paper is that in "anomalous projection" there are no "corresponding visual axes" and that it

is, therefore, a "type of binocular projection without retinal correspondence." He has found that not one retinal element but a large retinal area of the squinting eye may have temporarily "corresponding visual axes" with the principal visual axis of the fixating eye and that there is thus in "anomalous projection" a type of retinal correspondence which is not fixed but variable. The variability and instability of the sensorial retinal relationship in anomalous correspondence is a well known phenomenon, emphasized by all good writers; it is an essential characteristic of the anomalous retinal relationship and has led Tschermak to pertinent criticism of the terminology, as will be seen in the last section of this paper. Harms even stated that this variability may be an imperfect substitute for fusional movements.

The question, however, is how Verhoeff showed this instability and whether it justifies his sweeping conclusions. Verhoeff used two methods to prove his point. One was the "subjective cover test," in which the patient has to state whether the fixated object point, situated at 6 meters, appears changed or unchanged in its position when a cover is quickly transferred from one eye to the other. The other he described as follows: The patient fixates (either at 6 meters or at 10 cm.) an object point with one eye. Other objects are then placed anywhere along the visual axis of that eye, and the eyes are alternately covered. Again, the various object points appear "in the same place in space no matter from which eye they are seen." Thus, "although an object is moved along a monocular visual axis of one eye and the position of its retinal image in the other eye constantly changes, the two images continue to correspond."

There are various objections, possibly of minor importance, which could be raised to these experiments, which are described only in principle. The principal objection, however, that they do not test retinal correspondence at all, is valid in any case. Aside from the fact that the condition of the sensorial retinal relationship can be determined only by simultaneous stimulation of selected retinal areas, Verhoeff's tests relate to the absolute, not the relative, localization. And these two, as has been pointed out repeatedly in this paper, must be strictly separated. The condition of the sensorial retinal relationship is determined not by the localization of an object point in subjective space relative to the coordinates of this space and to the subjective coordinates of the observer's head and body, but by the localization relative to each other of stimuli reaching simultaneously specified areas of the two retinas. Verhoeff's criticism of the after-image test, that the "criteria of distance are inadequate for each eye," is therefore without any foundation.

That Verhoeff did not distinguish absolute and relative localization is borne out by the fact that throughout the paper he spoke of "correct" and "incorrect anomalous projection." He stated explicitly that "since the term anomalous as applied to binocular projection refers only to the

type of projection, it carries no implication as to the correctness of the projection. Obviously, there may be anomalous correct or incorrect projection, depending on the monocular projection."

At the bottom of this confusion of egocentric and relative localization is the fact that Verhoeff espoused the projection theory of spatial localization. In a significant passage, Verhoeff stated:

> In the case of retinal correspondence, monocular depth criteria (such as size) have nothing to do with determining the direction of any monocular or binocular visual axis, that is to say, with determining the apparent angular direction of any object. In the case of anomalous projection, however, monocular depth criteria derived from the squinting eye, even when binocular criteria are removed by means of a suitable screen, can determine the apparent direction of an object as seen from only that eye in binocular vision. As concerns any object well within the binocular field, the visual axis of a retinal image in the squinting eye intersects innumerable visual axes of the fixing eye. To which of these intersections the image is projected, and hence in binocular vision along which axis of the fixing eye it is projected, monocular depth criteria derived from the squinting eye can determine. Thus whether *A* and *B* . . . are projected to their actual locations or to the crossing point *P* can depend solely on monocular depth criteria. This analysis reveals one of the fundamental distinctions between the projection of a person with fixed retinal correspondence and that of a person with anomalous projection.

I believe this lengthy analysis has shown that there is nothing in Verhoeff's paper which would compel one to accept his statement that there are "no corresponding visual axes" in anomalous retinal correspondence or to justify his criticism of the expression "anomalous correspondence adapted to the angle of squint," made on that basis. The concept does not have to be relinquished that in many squinters a common visual direction between *de norma* disparate retinal elements can be shown to exist at a given time and under the test conditions. Even though this relationship may not have the stability of the normal correspondence, it is in some cases stable enough to persist quantitatively over many years, even if the relative position of the eyes is changed by operation. These cases, together with the different types of cases in which normal and anomalous correspondence coexist, afford the most conclusive clinical evidence against Verhoeff's point of view. He recognized this, of course, and stated that "no doubt these [cases of post-operative triplopia] are usually due to persistence of the old anomalous projection, now incorrect, along with the development of new and correct projection." How an anomalous projection which allegedly consists in an absence of "binocular visual axes" can persist after an operation which has straightened the eyes and produce a monocular diplopia in which one image is at a distance corresponding to the old angle of squint is entirely inexplicable, and Verhoeff made no attempt to explain it. Nor is it clear how this and similar phenomena could at all be interpreted on the basis of a theory according to which spatial localization occurs by projection along the lines of direction.

The theory of common visual directions also explains some interesting observations on the ϕ phenomenon in patients with strabismus, which were published by Verhoeff in 1940.[70]

The ϕ phenomenon, so named by Wertheimer,[71] consists in an apparent movement which occurs when different groups of retinal elements are successively stimulated in a specified way and at specified time intervals. "Moving" advertising signs have familiarized every one with the phenomenon. It occurs not only in monocular and binocular vision, but also when the stimuli are successively presented to different regions of the retinas of the two eyes. Verhoeff had the ingenious idea to test the ϕ phenomenon in patients with convergent and divergent strabismus by exposing a luminous target for one-twentieth second first on the fovea of one eye and then an identical target on the fovea of the other eye. The two targets were placed at 60 cm. from the observer and separated by his angle of squint. In these circumstances, an observer with normal retinal correspondence should not see a movement, but if he has anomalous correspondence a movement should occur in accordance with the angle of anomaly.

Verhoeff found that the ϕ phenomenon was indeed readily elicited in all 13 patients whom he examined. In addition, he performed an experiment on a patient with facultative divergent squint in which he placed the luminous targets so that the one seen by the left eye fell 4 arc degrees temporal to the left fovea and the one seen by the right eye fell 8 arc degrees temporal to the right fovea, both when the patient's eyes were dissociated and when he fixated binocularly. In the first instance the two luminous targets were to the right of a rod placed at 60 cm. from the patient in his median plane; in the second instance the target seen by the right eye was moved to the left of the fixation rod. The target A (seen by the left eye) was always illuminated first. Both when the eyes of the patient were dissociated and when he fixated binocularly, an apparent movement from A to B (seen by the right eye) occurred; only in the first case the movement was from left to right; in the second, when target B was to the left of the fixation rod, from right to left.

Verhoeff did not explain the result of this experiment but used it as a basis for a short criticism of Wertheimer's theory of the ϕ phenomonon. Actually, the explanation is quite simple and in no way affects Wertheimer's theory. The fact, stressed by Verhoeff, that the external criteria were interpreted correctly in each instance is of no significance.

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70. Verhoeff, F. H.: Phi Phenomenon and Anomalous Projection, Arch. Ophth. **24**:247 (Aug.) 1940.

71. Wertheimer, M.: Experimentelle Studien über das Sehen von Bewegungen, Ztschr. f. Psychol. **61**:161, 1912.

The ϕ phenomenon is based on the successive stimulation of retinal elements having different visual directions. Verhoeff did not recognize the importance of the visual directions, which is why the results of the experiment appear puzzling. Assuming that the patient had an anomalous retinal relationship when his eyes were dissociated, the visual direction of the retinal point, *b*, on which the image of target *B* falls would have approximately the visual direction β. In the cyclopean eye a would be to the left of β, and the successive stimulation of *a* and *b* would produce an apparent movement from left to right (fig. 9*A*). When the patient fixated binocularly, he used presumably normal correspondence, as happens so often in cases of facultative divergent strabismus,[72] and the visual direction of a in the cyclopean eye would now be to

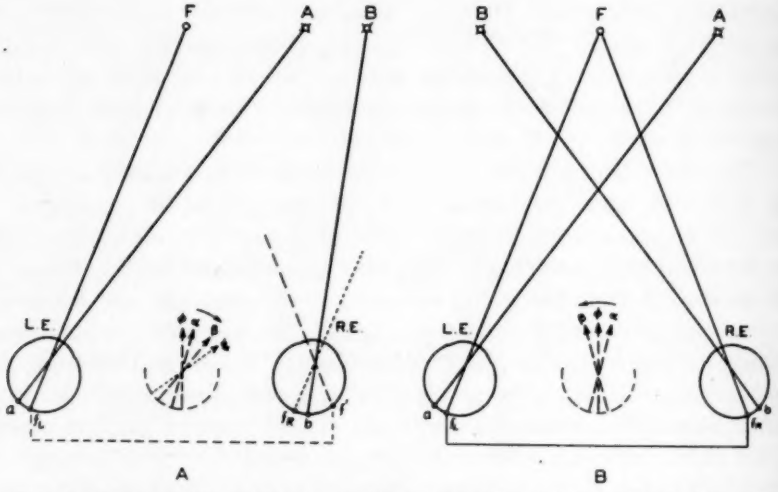

Fig. 9.—Diagram illustrating a possible explanation of Verhoeff's ϕ phenomenon experiment in a case of facultative divergent strabismus.

the right of β (fig. 9*B*). Consequently, the successive stimulation of *a* and *b* would produce an apparent movement from right to left. This would not occur if the patient should continue to localize according to his anomalous correspondence while fixating binocularly. The position *in space* of the targets does not influence the direction of the movement; it is determined by the visual directions of the stimulated elements.

Verhoeff's observations would thus confirm beautifully the theory of retinal correspondence adopted in this article. Unfortunately, Verhoeff's paper is very short and lacks much pertinent information. For

72. Burian, H. M.: Motility Clinic: Intermittent (Facultative) Divergent Strabismus; Its Influence on Visual Acuity and the Binocular Visual Act, Am. J. Ophth. **28**:525 (May) 1945.

instance, he did not state whether or not his patients had anomalous correspondence; he did not attempt to place the targets at the angle of anomaly (in which case no movement should occur if the theory is correct). His paper can thus be regarded only as a preliminary study, but it certainly opens up a new and extremely interesting method of investigating the normal and anomalous retinal relationship.

The difficulties arising from the lack of familiarity with the older literature and from the confusion in the more recent literature on anomalous correspondence are clearly shown in a paper by Burri.[73]

Miss Burri examined the question as to what constitutes anomalous correspondence and concluded from the writings of Mayou, Pugh and Travers that the current opinion appeared to be that the objective and subjective angles have to coincide for the correspondence to be normal. This, Burri stated, puts the theory of anomalous correspondence on anatomic or "anatomicoretinal" grounds, but none of the authors have given a "clear explanation of the anatomic function of abnormal correspondence. . . . The theory of abnormal retinal correspondence has been developed from the basic hypothesis that exact retinal correspondence is an objectively demonstrable and invariable fact" and stands and falls with the validity of the basic hypothesis.

Is, then, Miss Burri asks, normal correspondence, and consequently anomalous correspondence, an objectively demonstrable fact, or are they subjective inferences?

Her search of the neurologic literature remained inconclusive. Some neurologic findings point toward a certain correspondence between retinal and cortical areas; yet considerable equipotentiality and mass action exist. The study of the horopter is also unsatisfactory, since it is not "objective" but is based on "subjective inferential data."

In this paper, in the beginning of the section on the methods for the determination of anomalous correspondence, it was mentioned that there are ingenious laboratory methods for the determination of the distribution of the corresponding retinal points. The determination of the empiric longitudinal horopter is one of them. If Miss Burri had studied the work of Tschermak-Seysenegg,[1] she would have found ample information on the criteria of correspondence. She would also have found that what she terms "subjective inferential data" are data of the highest accuracy and that the methods of the exact subjectivism [2] are in principle the only methods by which one can ever learn something about the subjective phenomena of correspondence and visual localization.[11] Whether the anatomic and physiologic correlatives of these phenomena are a retinocortical point to point relationship, or whether such factors as mass

73. Burri, C.: The Concept of Abnormal Retinal Correspondence: A Theoretical Analysis, Arch. Ophth. **19**:409 (March) 1938.

action and equipotentiality are involved, is of great interest in itself but has no bearing on the theory of retinal correspondence.

I believe that in the light of this knowledge she would probably have considered her own experimental evidence somewhat more critically. She studied three groups of patients: 40 without muscular imbalance, 40 with either esophoria or exophoria and 40 with esotropia or exotropia. All these subjects were tested on the synoptophore and were allowed to adjust the instrument so that the two pictures were superimposed. The figures thus obtained were compared with the figures resulting from the screen test, the parallax test and the perimeter test. Five or six trials were given each subject, and the largest and smallest deviations obtained with the synoptophore test and with the other tests were tabulated. The averages are given in a table for the three groups. The deviations are assumed to be a measure of the retinal correspondence.

Miss Burri found that none of the groups showed "exact retinal correspondence"; the patients without muscular imbalance showed essentially the same deviation (maximum, about 3 degrees; minimum, 1 to 2 degrees), and the patients with strabismus, a somewhat larger deviation (maximum, 6 to 7 degrees; minimum, about 4 degrees).

It is quite apparent that this rough experiment can in no way influence the theory of retinal correspondence. Too many sources of error enter into the settings, such as size of image, fusional amplitudes, instrument convergence and single vision with Panum's areas; it is, however, surprising that all 40 patients with strabismus were able to superimpose macularly seen images and that there was no more than a deviation of 4 to 7 degrees from the objective angle. Without more information about such factors as the type of target and the selection of the strabismic cases, a real evaluation of the data is impossible. In any event, they do not justify the adoption of the empiristic theory of retinal correspondence, which Miss Burri again proposed.

In 1939 there appeared Chavasse's book on squint,[27] which is bound to have a profound influence on future thinking on the subject of strabismus. Written—even overwritten—in a refreshingly unorthodox style, dominated by one central idea, the book has the advantage of being an organic whole and has the earmarks of a work of art. New bottles are made, as Chavasse said, to hold the new wine of Sherrington, Magnus and Pavlov. Yet I believe that the book, so persuasively and brilliantly written, is dangerous to those who have not taken a long draft of the "old wine" of Helmholtz, Hering, Tschermak-Seysenegg, Javal and Bielschowsky.

All varieties of squint, Chavasse argued, appear as perversions or subversions of the normal binocular reflexes by various obstacles during and after the developmental period. Ontogeny, phylogeny, anatomy and

physiology are reviewed from this standpoint, and a new pathology of the binocular reflexes is evolved. In such a system, anomalous, or, as Chavasse called it, secondary, retinal correspondence naturally plays a large role. In fact, the concept of correspondence is extended, and even overextended, to a point where the whole concept becomes blurred, and the state of squint is defined as "a state of secondary correspondence." There is alleged to be a state of primary (or normal) motor correspondence, reflected in the correct position of the eyes; a primary (or normal) retinal correspondence, reflected in identical retinal projections, and a primary (or normal) proprioceptive correspondence between the two uniocular proprioceptions, reflected in identical projections of the two foveovisual axes.

It is, of course, impossible to go into the wealth of detail of Chavasse's book, and I must restrict myself here to his statements relating to the theory of anomalous retinal correspondence.

Chavasse distinguished clearly between relative and egocentric spatial localization. According to him, the former is determined by the retinal correspondence; the latter by the proprioceptive correspondence. But he expressed the belief that "secondary retinal correspondence" can be properly appreciated only if "secondary proprioceptive correspondence" is added, the whole constituting a "perverted binocular fixation reflex."

It must be said, first of all, that "proprioceptive correspondence" is at best a dubious idea. It has been doubted, for good reason, that proprioception, particularly ocular proprioception, is a factor in spatial localization in man. Egocentric localization, on the other hand, about which little is known in concomitant strabismus, does not appear to be closely related to the behavior of retinal correspondence.

Chavasse's argument, though clothed in the language of reflexology, really resolves itself into the old projection theory, aided by the concept of the "muscle sense." And with it there remain all the difficulties of explaining the sensorial phenomena observed in concomitant strabismus. This is particularly evident in Chavasse's attempt at interpreting "monocular diplopia" and "binocular triplopia." To him, "the image of the erstwhile squinting eye is being projected in two directions, the normal retinal and the secondary proprioceptive." This most unsatisfactory explanation of a visual sensation by proprioception independent of a second visual sensation by retinoception was not clarified by Chavasse and, I believe, cannot be clarified.

Nor did Chavasse understand Hering's concept of corresponding retinal points. He stated that Hering stressed the anatomic correspondence heavily but that this anatomic correspondence is by no means exact. As proof, Chavasse cited the Kundt partition experiment and the deviation of the subjective from the objective vertical. Thus,

Chavasse, by substituting an assumption which was not made [74] (a mathematical distribution of corresponding points), used the very argument on which exact subjectivism is based and then concluded:

> . . . allowance for the disparity is made, and can only be made, in virtue of a mechanism which is based upon proprioception of the state of version and vergence of the eyes, because the degree of disparity varies with this varying state.

The degree of disparity does not vary with this varying state. The conclusion to be drawn from the disparity between objective and subjective space is that the position of the corresponding points can be determined only by subjective methods.[11] It cannot be stressed too strongly that it is here that the clue to the understanding of anomalous correspondence lies.

To Chavasse, however, both normal and anomalous correspondence were conditioned reflexes. If the position of the eyes is such that the lines of gaze intersect in the fixation point, the proper habit in the use of the eyes will be established. This proper habit is the localization of the stimuli reaching the two foveas in identical subjective visual directions. If the lines of gaze do not intersect in the fixation point, the reflex is perverted: A common visual direction is established between the fovea of the fixating eye and an eccentric retinal element. With the passage of time, both the normal and the perverted conditioned reflexes become unconditioned, or automatic. From this theory Chavasse deduced his therapeutic principle: the early removal of motor or sensory obstacles which may produce the perversion or prevent the establishment of the normal binocular reflexes. Once the perverted binocular reflexes have become automatic, they cannot be normalized by any therapeutic procedure. Because of this, Chavasse was absolutely skeptical of orthoptic fusion training in any form.

To extend the concept of reflex to include, on the effector side, purely subjective phenomena may be accepted by the behaviorist school of thought. To me, the concept of reflex becomes devoid of meaning by this extension. Where there is no motor or secretory effect, there is no reflex, conditioned or otherwise. To include subjective phenomena in the objective sphere by making them the direct end result of reflex happenings makes the truly scientific investigation of either sphere impossible.

Chavasse's book must be read with discrimination. But it offers, in spite of its basic shortcomings, stimulating ideas about anomalous correspondence, its clinical significanace and its determination.

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74. Hering stated explicitly: "Each visual direction is an imaginary mathematical line. But since vision is by no means mathematically exact, the visual directions may *in praxi* not be considered as mathematically exact. They are approximate determinations fluctuating within certain limits." (Hering,[9] 1862, book 2, p. 159.)

A paper by Hamburger [75] is apparently of importance in the theory of anomalous correspondence. Unfortunately, because of the prevailing conditions, I was unable to procure the original paper, which was published by *Albrecht von Græfe's Archiv für Ophthalmologie,* and I have only a short abstract of Hamburger's presentation before the Ophthalmological Society of Vienna. It seems from this abstract that in examination of patients with strabismus Hamburger combined the synoptophore method with an after-image method, thus permitting a direct check on the behavior of the visual directions. He concluded that changes both in the angle of squint and in the angle of anomaly may cause a change in the visual directions. But he also found that the change from normal to anomalous correspondence is gradual. When first degree pictures are presented, there is anomalous correspondence and the after-images are separated; with dissimilar patterns, owing to the compulsion to fusion, the eyes straighten and the after-images approach each other, forming a cross over the fused haploscopic image. Hamburger did not believe that normal and anomalous correspondence coexist, as was assumed by Bielschowsky in the explanation of cases with monocular diplopia. The movement of the after-images observed by Hamburger's patients could be explained on the basis of the ϕ phenomenon,[79] but until the details of his investigations are known it is not possible to evaluate his conclusions.

In 1942 Werner [76] attempted to demonstrate that the same principles can be shown to be effective in an abnormal retinal relationship and in normal binocular vision. He rejected what he claimed to be Hering's definition of corresponding points and introduced a "dynamic" concept of stereopsis, according to which binocular stereopsis is connected with a "functional change of projection," or functional displacement. The "change of projection," such as occurs in anomalous correspondence, was also thought to signify a functional displacement, and Werner further stated that analogous changes of correspondence occur in normal vision. It is impossible to present here fully the reasons that Werner's conclusions are fallacious; all that can be stated is that his premises are not sufficiently well founded to permit the far reaching conclusions which he has drawn and which deeply affect the theory of binocular vision. In another paper Werner's experiments will be dealt with in some detail.[77]

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75. Hamburger, F. A.: Haploskopische Untersuchungen an Schielenden, Klin. Monatsbl. f. Augenh. **108**:235, 1942.

76. Werner, H.: Binocular Vision: Normal and Abnormal, Arch. Ophth. **28**:834 (Nov.) 1942.

77. Ogle, K. N., and Burian, H. M.: The Stability of the Spatial Values of the Retina and the Theory of Stereopsis, to be published.

The most recent paper on anomalous correspondence is that by Swan.[78] He objected on three grounds to the definition of anomalous correspondence as a condition in which the fovea of one retina and an eccentric element of the other acquire a common visual direction, as given by Lancaster.[6] He stated, first, that such a functional relation can be demonstrated in few patients with anomalous retinal correspondence. This is contrary to fact. In virtually every case it can be shown by the double image test that such a relationship does exist. Secondly, Swan claimed that adoption of this definition is not expedient, because it may have misled ophthalmologists to believe that the condition is rare. This statement he based on the fact that in a series of 100 consecutive patients with esotropia seen in the State University of Iowa Clinics in 1935, only 3 were suspected of having anomalous correspondence. The test was performed with

> an illuminated Brewster-Holmes type of prism stereoscope so adjusted that when one target was fixated by the fovea of the nonsquinting eye, the other target stimulated that peripheral retinal area of the squinting eye which, according to the aforementioned definition, could become a functionally corresponding point. Correspondence was considered abnormal only if the two objects were superimposed.

It is true, as Swan stated, that this test is fallacious—rather, that it has its limitations—but this does not substantiate Swan's claim that the definition is fallacious. The definition does not state which retinal area of the squinting eye has common visual directions with the fovea of the fixating eye; i. e., it is not restricted to cases of harmonious anomalous correspondence, as Swan seemed to imply in the foregoing citation, nor does it state that the patient will necessarily perceive simultaneously or fuse at the angle of anomaly.[79] Finally, Swan, in accordance with Harms, Travers and others, found that there is a region of suppression in the area of the retina of the squinting eye which supposedly has a common visual direction with the fovea of the fixating eye. How, he asked, can the fovea of the fixating eye become a functionally corresponding point with a suppressed retinal area in the squinting eye? This situation has been discussed in a previous section of this paper. It was stated that this typical interrelation between suppression and anomalous correspondence may well lead to an explanation of the origin of anomalous correspondence. In any event, as was said before, the existence of such a relationship can always be demonstrated in the double image test.

For the rest, Swan recognized that anomalous correspondence is a process of adaptation and that the findings may vary with the type

78. Swan, K. C.: Definition of Anomalous Retinal Correspondence, Am. J. Ophth. **28**:58, 1945.

79. Some writers, to be sure, say that the patient uses the macula of one eye with the nonmacular area of the other eye.

of test used, and he advocated intensive orthoptic training immediately after operation to establish normal correspondence before an anomalous correspondence adapted to the new deviation develops.

2. MONOCULAR DIPLOPIA AND BINOCULAR TRIPLOPIA

In 1924 Fischer [80] reported a case of binocular triplopia occurring after operation for convergent strabismus. The formerly deviated eye had a corrected visual acuity of 0.1. Fischer accepted Bielschowsky's [81] explanation of the phenomenon for his own case and emphasized that it was a good example of the adaptability and elasticity of the sensorial apparatus.

Gredstedt [82] also based the explanation of a case, which he briefly reported, on the coexistence of normal and anomalous retinal correspondence.

The whole subject of anomalous correspondence was well stated by Purdy [83] in connection with a case of monocular diplopia. This author studied in a psychologic laboratory an 18 year old student with strictly alternating convergent strabismus (visual acuity of 20/15 in each eye with a —1.25 D. sphere for the right eye and 0.25 D. sph. $\frown$ + 0.25 D. cyl., axis ? for the left eye), who had been operated on at the ages of 5 and 14 years. There were a small residue of convergent strabismus and a hypertropia. The observer had permanent spontaneous diplopia, which he was able to disregard; the distance of the spontaneous double images corresponded to the angle of squint (normal correspondence). Under appropriate conditions, with either eye alone, there was monocular diplopia; the second image was to the right when seen with the left eye and to the left when seen with the right eye (indicating anomalous correspondence).

Purdy fully accepted the classic explanation of the phenomenon and stated the belief that his case furnished added support to the idea that the normal retinal correspondence is congenitally established but that it differs from others in that the monocular diplopia can be produced with either eye. Purdy assumed that the anisometropia in his case prevented the development of marked ocular dominance and hence made possible the acquisition of two anomalous systems.

It is not necessary to assume two anomalous systems to explain the case. The "anomalous system," the angle of anomaly, is the same no matter which eye fixates. Just as in any other case of convergent

80. Fischer, E.: La neutralisation régionale dans un cas de triplopie binoculaire postopératoire chez un strabique, Ann. d'ocul. **161**:208, 1924.

81. Bielschowsky, A.: Ueber monokuläre Diplopie ohne physikalische Grundlage nebst Bemerkungen über das Sehen der Schielenden, Arch. f. Ophth. **46**: 143, 1898.

82. Gredstedt: Ueber einäugiges Doppeltsehen, Ztschr. f. Augenh. **72**:243, 1930.

83. Purdy, D. M.: Double Monocular Diplopia, J. Gen. Psychol. **11**:311, 1934.

strabismus with anomalous correspondence, each fovea had acquired a common visual direction with an eccentric (nasal) element of the other retina. The distinctive feature of the case is that both the normal and the anomalous visual direction coexisted, producing monocular diplopia.

An interesting observation was reported by Purdy. When he attempted the experiment of color mixture with his subject, color mixture was never obtained, nor did the colors display rivalry or appear to be lying one behind the other. Instead, the two colors were seen simultaneously in the same place. Purdy concluded that there is a remarkable degree of independence between the binocular fields. The phenomenon is comparable to the one which I described,[15] in which patients with permanent spontaneous diplopia saw "two objects in the same place" when one object, such as a pencil, was brought into the point of intersection of the patient's lines of gaze.

In their book on concomitant strabismus, Malbrán and Adrogué[84] reported 3 cases of binocular triplopia. Another case was reported by Adrogué and Lagos.[85] These authors were in agreement that the phenomenon is due to the persistence of the anomalous correspondence coexisting with the normal correspondence. They seemed to feel, however, that the monocular diplopia is not due to the localization in two visual directions of the foveal stimuli of the deviating eye, but rather, that it is the result of the visual direction of the eccentric element in the deviating eye which corresponds anomalously with the fovea of the fixating eye somehow coming into consciousness. Thus they stated that in binocular triplopia there are three images: one perceived by the fovea of the fixating eye, another perceived by the fovea of the deviating eye (in normal correspondence with the other fovea) and a third perceived by the region in the deviating eye which has a common visual direction with the fovea of the fixating eye. Since no stimulation of that area occurs in these cases (for instance, in the double image test), no "perception" can take place, and this interpretation is therefore without basis in fact. Sverdlick[26] expressed the opinion that the cases of Malbrán and Adrogué are not typical and convincing cases of monocular diplopia but gave no reason for his statement.

Cass[86] made an interesting contribution to the problem of monocular diplopia. She was able to produce the phenomenon on the synoptophore in a surprisingly large number of cases, namely, in 33 out of 70. In

84. Malbrán, J., and Adrogué, E.: Estrabismo, Buenos Aires, El Ateneo, 1938; Sobre diplopia uniocular, Arch. de oftal. de Buenos Aires **13**:140, 1938.

85. Adrogué, E., and Lagos, E. J. J.: A propósito de un caso de diplopia permanent. postoperatoria (estrabismo), Arch. de oftal. de Buenos Aires **13**:512, 1938.

86. Cass, E. E.: Monocular Diplopia Occurring in Cases of Squint, Brit. J. Ophth. **25**:565 (Dec.) 1941.

some of the cases (51.2 per cent) she could elicit it only by placing the arms of the synoptophore at the subjective angle; in others (15.2 per cent), only by placing the arms at the objective angle, and in a third group (33.3 per cent), by placing the arms at either angle. The synoptophore targets were fused in all these cases, but on flashing, a second image appeared in the uncrossed or the crossed position, according to whether the monocular diplopia was produced at the subjective or the objective angle. The average age at the onset of strabismus was lower in the group in which monocular diplopia could be elicited than in the group in which it could not. Patients with anomalous correspondence only, and some degree of binocular vision with it, usually had monocular diplopia, but those whose binocular vision was rudimentary had no binocular diplopia. Patients with both normal and anomalous correspondence, when the normal correspondence was strong, usually had no monocular diplopia. In the majority of cases in which monocular diplopia could be elicited there was an equal degree of binocular vision whether the patient used the eccentric point or the macula of the deviated eye with the macula of the fixating eye.

In 1943 I published an observation [42] which I consider to be related to binocular triplopia. In the case in question the patient, who had a facultative divergent strabismus, presented both normal and anomalous correspondence. On occasions, however, when the double image test was administered, the patient reported that he saw the two lights in a slightly uncrossed position (anomalous correspondence); yet at the same time he had the "mental impression" that the separation between the two lights was much greater and that the second image "should be" in a position corresponding to a crossed diplopia of 12 to 14 arc degrees (normal correspondence).

3. CLINICAL APPLICATION: ANOMALOUS CORRESPONDENCE AND ORTHOPTIC TREATMENT

In 1927 Fischer [87] stated that orthoptic exercises can be successful only if there is normal retinal correspondence. Otherwise, exercises should be discontinued because of the danger of postoperative paradoxic diplopia. Fischer determined the state of the retinal correspondence with the amblyoscope and found an anomalous relationship in 50 per cent of the cases.

Braun,[24] for the same reason as Fischer, warned against the use of postoperative exercises in cases of deeply rooted anomalous correspondence. In an exhaustive study, carried out under the direction of Tschermak, he reported on a series of patients with convergent

87. Fischer, E.: Die Bedeutung der anomalen Korrespondenz der Netzhäute bei Uebungen der Schielenden im Binokularsehen, Russk. oftal. j. **6**:225, 1927; reviewed, Klin. Monatsbl. f. Augenh. **79**:706, 1927.

strabismus, whom he divided into three groups: The first group (8 patients) had normal correspondence; the second (5 patients) showed both normal and anomalous correspondence, and the third (24 patients) had only anomalous correspondence. The prognosis as to the spontaneous restoration of binocular vision was good in the first group, doubtful in the second and very poor in the third.

The first to discuss anomalous correspondence in the American literature was Moncreiff.[88] He gave a short but excellent account of its essence, its methods of determination and the earlier literature, in a paper dealing also with other disturbances of the visual function in concomitant convergent strabismus. Moncreiff did not report any personal experiences; but he recognized the types of harmonious and unharmonious anomalous correspondence (the latter having developed out of the harmonious type by reduction in the angle of squint), described the areas of suppression found in the various groups and expressed agreement with the view that anomalous correspondence represents a sensorial adaptation to the squinting position of the eyes.

In 1934 Hine[89] stated that anomalous correspondence, determined with the synoptophore, exists in 70 per cent of squinters. He expressed the opinion that fusion training should not be given without regard to this, since otherwise the anomalous relationship may be encouraged. In the interest of restoration of binocular vision, Hine recommended operation prior to the age of 7 years.

In a paper on the possibilities of orthoptic training, published also in 1934, Guibor[90] was not concerned with anomalous correspondence. His paper is mentioned here only because he called the angle of squint the "angle of anomaly," a terminology which is not recommended because of the confusion which such a use of the term would create.

Pugh[91] reported that in dealing with 400 patients with strabismus she found anomalous correspondence in 169 (42 per cent) and normal correspondence in 226 (56 per cent). Of those with anomalous correspondence, 73 per cent had alternating squint and 27 per cent unilateral squint; of those with normal correspondence, 83 per cent had unilateral and 17 per cent alternating squint. Taking into account various sources of error, Pugh concluded that about 50 per cent of the squinters acquire anomalous correspondence.[92]

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88. Moncreiff, W. F.: Disturbances of Visual Functions in Concomitant Convergent Squint, with Special Reference to Retinal Incongruity, Arch. Ophth. **2**:179 (Aug.) 1929.

89. Hine, M. L.: The Orthoptic Treatment of Squint, Brit. M. J. **1**:329, 1934.

90. Guibor, G. P.: Some Possibilities of Orthoptic Training, Arch. Ophth. **11**:433 (March) 1934.

91. Pugh, M. A.: The Significance of False Projection in Squint, Proc. Roy. Soc. Med. **27**:1615, 1934.

It is of interest to note that Pugh mentioned vertical anomalous correspondence and that in some cases she even attributed ocular torticollis to it. She discussed, furthermore, the significance of anomalous correspondence with regard to the postoperative result and stated that a patient whose eyes were straightened while he had anomalous correspondence may do one of three things:

(*a*) He may, finding the visual axes parallel, develop a true projection and fuse with his eyes straight.

(*b*) He may pass through a transitional stage when he learns to readjust his projection so that he eventually adapts himself to the new position of the eyes. During this transition there is a false diplopia; in other words, a diplopia due not to faulty position of the eyes but to faulty projection of the visual images in space. He attempts to fuse the images with a false projection, and before the new projection is developed there is a tendency to recover some of the original deviation.

(*c*) He may show no sign of modifying his false projection, but retains it. Such a patient suffers from a troublesome false diplopia and in his efforts to overcome this symptom he reverts more or less to his original deviation.[91]

In a paper on the classification of concomitant strabismus, Pugh [93] spoke of anomalous correspondence only in connection with "fusion defect squints." [94] In the larger proportion of cases of strabismus of this type "false projection" develops. This gives the erroneous impression that anomalous correspondence occurs only in cases of this type. She further noted that the mechanism by which "false projection" is obtained appears to be chiefly cerebral, but that there is a specialized hypersensitive zone lying between the macula and the false projection spot. In a case of alternating squint, the spot on the retina of the deviated eye which corresponds in position to the macula of the fixing

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92. It is of interest to compare these percentages with the old figures of F. Mügge (Ueber anomale und normale Sehrichtungsgemeinschaft bei Strabismus convergens, Ztschr. f. Augenh. **16**:110, 1906), who found that of his patients with anomalous correspondence 61.5 per cent had alternating squint and 27.4 per cent unilateral squint. P. A. Jaensch (Die Dauererfolge der operativen Therapie des Ein- und Auswärtsschielens, Klin. Monatsbl. f. Augenh. **72**:86, 1924) found that 235 (83 per cent) of 283 patients with convergent strabismus and 53 (49 per cent) of 108 patients with divergent strabismus showed anomalous retinal correspondence. In the light of the old and more recent figures, Verhoeff's statement [10] that it is commonly assumed that "anomalous projection" exists only in unusual cases is not understandable.

93. Pugh, M. A.: A Classification of Cases of Concomitant Strabismus Based on the Etiological Factor, Brit. J. Ophth. **18**:466, 1934.

94. Among 500 cases Pugh found (1) squint due to refraction error in 62 per cent, (2) squint due to fusion defect in 15 per cent, (3) psychologic squint in 21 per cent and (4) squint due to physical defect in 2 per cent. The discussion preceding the figures in the paper is brief and incomplete; the classification appears artificial, and hence the figures are not meaningful.

eye appears to acquire a special localizing power in conjunction with the opposite macula. As to treatment, Pugh suggested that in a case of "fixed false projection" the best procedure is to try to develop "true projection" and fusion by training and then to operate. Training in a case of alternating squint with "fixed false projection" is tedious unless the treatment is aided by surgical intervention. She also warned that "false," or paradoxic, diplopia is a stubborn condition, not easily corrected by training. The patient, she alleged, tries to fuse the images and, to do so, turns the eye back toward the original position of squint, and many of the disappointing results of operation are due to this state of binocular vision.

Chavasse,[46] like Pugh, expressed the belief that the persistent absence of normal retinal correspondence, together with easily elicited anomalous correspondence, signifies that after operation there may be troublesome diplopia and paradoxic reflexes which tend to interfere to a greater or lesser degree, and for a longer or shorter period, with the result—even the merely cosmetic result—of operation. Chavasse was also pessimistic about the results of fusion training in cases of anomalous correspondence if the patient is over 6 years of age and if repeated tests by various methods fail to reveal any trace of normal correspondence. He considered these patients incurable by any form of treatment.

Goulden [95] stated that false projection may occur as an extremely serious complication of an operation for strabismus.

Miss Smith [35] also found that preoperative correction of an anomalous correspondence by orthoptic exercises is essential in insuring a good surgical result. She supported her contention by rather impressive statistical data. Of 30 patients who were operated on before normal correspondence was established, the eyes of only 4 remained straight; in contrast to this, the eyes of 17 of the 19 patients in whom normal correspondence was established prior to the operation remained straight. On the other hand, of the 25 patients who had to begin with normal correspondence and were operated on, the eyes of 22 remained straight.

Statements about the deleterious influence of anomalous correspondence on the operative result are frequently heard,[96] and it is therefore worth while to stop for a moment to consider what they imply. They imply that after an operation for strabismus which has achieved parallelism or near-parallelism of the visual lines, the eyes may return more

95. Goulden, C.: The Principles of Orthoptic Training, Tr. Ophth. Soc. U. Kingdom **55**:576, 1935.

96. T. Keith Lyle,[54] for instance, spoke of "cases where a course of orthoptic treatment, in which binocular stimulation has been given at the subjective angle of squint, has been undertaken, with the result that after a carefully planned operation which has reduced the angle of deviation to 0°, the squinting eye has, in a few days after the pads have been removed, returned to its previously squinting position."

or less to their previous deviated position because of the persistent anomalous correspondence. This means that the motor conditions adapt themselves to the sensorial conditions; in other words, the old theory of Johannes von Müller, of incurable *strabismus incongruus,* is revived.

I do not believe that this pessimistic attitude is theoretically justified or practically borne out. In my experience with a very large number of cases of concomitant strabismus, I have never found anomalous correspondence a serious handicap to the obtaining of a good operative result. As compared with the large number of cases with anomalous correspondence treated by operation, the number of cases of troublesome postoperative spontaneous diplopia is negligible. The cosmetic result is just as good in cases with normal as in cases with anomalous correspondence. When the result was not satisfactory, I could almost always detect a mechanical reason for it. This applies to cases of normal as well as of anomalous correspondence.

In a paper published in 1935,[97] but not in a subsequent one published in 1941,[98] Feldman confused anomalous correspondence with aniseikonia. In the second paper he stated that he relied entirely on the synoptophore, since neither the congruence apparatus of Tschermak-Seysenegg nor the after-image test has proved satisfactory in the diagnosis and treatment of the conditions, because children are not always dependable in subjective tests. Feldman reported cures in about 50 per cent of his cases.

Penman [99] stated that in about 50 per cent of the cases of concomitant strabismus, mainly those in which the condition is of long duration and early onset and the angle is fairly large, anomalous correspondence is exhibited. In his opinion, treatment in cases of persistent anomalous retinal correspondence should be entirely cosmetic.

Much attention was given to anomalous correspondence by Malbrán and Adrogué.[84] The physiologic basis of binocular vision was discussed at great length, and the sensorial behavior in cases of concomitant strabismus was studied in detail. The authors expressed the belief that the sensorial behavior offers the best criterion for a rational classification of the cases of strabismus. They found anomalous correspondence in 85 (or 55 per cent) of 153 cases of convergent strabismus, normal correspondence in 60 (39 per cent) and mixed correspondence (preoperatively) in 8 (5 per cent). Of the 26 cases of alternating convergent strabismus out of the total of 153, normal correspondence was present in only 4, anomalous correspondence in 20 and mixed

97. Feldman, J. B.: Orthoptic Treatment of Concomitant Squint, Arch. Ophth. **13**:419 (March) 1935.

98. Feldman, J. B.: Clinical Observations on the Treatment of Squint, Arch. Ophth. **26**:38 (July) 1941.

99. Penman, G. G.: Treatment of Concomitant Squint by Orthoptic Methods: Some General Considerations, Brit. M. J. **2**:1019, 1937.

correspondence in 2. Thus the authors confirm the earlier statements that anomalous correspondence is particularly frequent among patients with alternating strabismus.

Cass,[61] in 1938, gave a historical survey of the problem of anomalous retinal correspondence and reported percentages found by her on the basis of examinations with the synoptophore. Her figures (in condensed form) are reproduced in table 2.

Some interesting observations on anomalous correspondence were reported by Dicke.[100] This author considered both normal and anomalous correspondence to be a habit mechanism, the latter established as the result of simultaneous stimulation of noncorresponding points. For the diagnosis, Dicke used the after-image test, the diplopia test and a major synoptophore. She found that the anomalous correspondence was more firmly established if it was evident in all three tests. In some

TABLE 2.—*Results of Examination on the Synoptophore in 500 Cases of Strabismus*

	Convergent Strabismus: 388 Cases (77.6%)		Divergent Strabismus: 107 Cases (21.4%)	Vertical Strabismus: 5 Cases (1%)
	Unilateral: 338 Cases	Bilateral: 50 Cases	All Types	++
Anomalous correspondence only	20.1%	54%	12%	
Normal and anomalous correspondence	22.2%	8%	8%	60%
Normal correspondence	49.1%	32%	67%	20%
Suppression	8.6%	6%	....	20%

cases the anomalous correspondence quickly yielded to normal correspondence by macular stimulation; sometimes after twenty to thirty minutes of this procedure even the after-image test showed a normal retinal relationship. Dicke looked on the prognosis in these cases as being favorable. As to the length of the treatment (constant occlusion and regular periods of orthoptic exercises several times a week), Dicke expressed the belief that failure to improve after four or five months constitutes a fair trial.

The preoperative and postoperative treatment of anomalous correspondence was also outlined by Mann.[56] She, too, emphasized the value of occlusion and stressed particularly the importance of directing the patient's attention properly during the exercises.

VII. TERMINOLOGICAL COMMENTS

It is apparent from many of the more recent papers in which anomalous correspondence is discussed that much of the misunderstanding and confusion is due to a lack of clarity in the terminology.

100. Dicke, D. E.: Anomalous Retinal Correspondence, Am. J. Ophth. **25**: 585, 1942.

It seems desirable, therefore, to conclude this paper with a few comments on terminology.

The oldest term used to designate an anomalous retinal relationship is "retinal incongruity" (incongruous retinas, strabismus incongruus). Introduced, I believe, by Johannes von Müller and used by von Graefe, it occurs occasionally in the recent literature (Moncreiff,[88] Feldman,[97] and others). This term should not be used. It is equivocal and gives rise to confusion, since it is properly used to designate physiologic and pathologic discrepancies existing in normal correspondence (which is why Feldman confused aniseikonia and anomalous correspondence).

Another term which is occasionally encountered is "false associated fixation" (Alabaster,[102] Lyle and Jackson[103]). This term is not well chosen: The association is not false; the fixation relates only to one eye; but the thought which probably promptetd the coining of the term may be correct.

I come now to the large group of terms which center around "projection" and "correspondence." The expressions "false and true projection" are widespread in the orthoptic literature, although some authors (Lyle and Jackson[103]; Smith,[85] and others) recognized that it may give rise to confusion "with the malprojection of one eye, present in paralytic squint" (Lyle and Jackson[103]). There are, however, stronger reasons that these expressions, and the analogous terms "normal and anomalous projections," should be relinquished. Not only do they lead to a confusion of absolute and relative spatial localization, but they embody a fallacious theory, the projection theory of spatial localization.

The terms "true" and "false" are also subject to criticism. I do not believe it to be good usage to speak of true and false images,[104] true and false angles, true and false projection, true and false correspondence. Because a phenomenon is subjective, it does not follow that it is false. There is nothing "false"—phenomenologically or otherwise—about a second image or any mode of localization in subjective space. Such second images, or a particular mode of localization, may be normal or anomalous, according to whether they follow the law of normal common visual directions. Spatial localization may be "correct" or "incorrect" (according to whether the phenomenal or the subjective appearance is in accordance with the objective localization of the stim-

101. Footnote deleted.

102. Alabaster, E. B.: Remarks on the Physiology of Convergent Concomitant Strabismus, Tr. Ophth. Soc. U. Kingdom **55**:321, 1935.

103. Lyle, K., and Jackson, S.: Practical Orthoptics in the Treatment of Strabismus, ed. 2, Philadelphia, The Blakiston Company, 1941.

104. It is regrettable that there is no English equivalent for the German term *Halbbild.*

ulating object points), but there is never anything "false" about it.[105] I believe, therefore, that the expressions "true" and "false" should be altogether abandoned and replaced by "normal" and "anomalous." In speaking of angles or spatial localization, "subjective angle" and "objective angle," or "subjective localization" and "objective position," should be used.

The term "anomalous correspondence" is probably more frequently employed now than any other term to denote an anomalous sensorial retinal relationship in strabismus. But this term, too, has its weakness, as was first pointed out by Tschermak-Seysenegg [80] and more recently, on similar grounds, by Verhoeff.[10] Tschermak-Seysenegg pointed out that the normal retinal relationship—the "normal retinal correspondence"—rests on an innate basis, is elementary and fixed and is connected with the system of horizontal disparity by which binocular depth perception or stereopsis is achieved. The "anomalous retinal correspondence," on the other hand, connects retinal elements of very different visual acuity; it varies under the influence of both exogenous and endogenous factors (i. e., it is not fixed, but unstable); depth perception does not come about through horizontal disparities on the basis of an anomalous retinal relationship, although rudimentary fusional movements may be elicited on that basis.

Consequently, Tschermak-Seysenegg reserved the expression "retinal correspondence" for the normal sensorial retinal relationship and coined the German term *anomale Sehrichtungsgemeinschaft* to indicate the one main characteristic of any anomalous sensorial retinal relationship, namely, that *de norma* disparate retinal elements have acquired, as an anomaly, a common visual direction. Tschermak-Seysenegg, therefore, did not accept terms such as pseudocorrespondence, pseudofovea or secondary correspondence (von Kries; Chavasse). Similar considerations apply to such expressions as "maculo-macular correspondence" (Chavasse) or, simply, "macular correspondence" (Cass [61]) or "maculo-pseudomacular correspondence."

There is no English equivalent for Tschermak-Seysenegg's *anomale Sehrichtungsgemeinschaft*. Attempts to translate it directly result in clumsy terms which are not appropriate for routine use. I have tried to evade this difficulty by adopting in the present paper the expression "normal and anomalous sensorial retinal relationship." This is a neutral expression which does not imply any theory and merely states a fact. It is, however, rather unwieldy, and I doubt, therefore, whether it will become generally accepted. I believe that, on the whole, the expression

105. It is, accordingly, normal for a person who places a meridional size lens at axis 90 in front of one eye to perceive under certain conditions a distortion of his subjective space—it would be anomalous if he did not—but he now localizes objects incorrectly.

"anomalous (retinal) correspondence," best satisfies the clinical needs and should be used, provided that the essential differences between "normal and anomalous correspondence" are kept in mind.

The terms "objective" and "subjective angle" have already been mentioned. The difference between the two represents the "angle of anomaly," or "angle of adaptation"; the former expression, being purely descriptive, is probably preferable. The term "quotient of perversion" (Chavasse) also implies a theoretic assumption (that both normal and anomalous correspondence are "reflexes") and is, therefore, not recommended.

The expressions "harmonious" and "unharmonious," or "subharmonious," anomalous retinal correspondence are convenient to indicate whether or not the angle of anomaly is equal to the angle of squint. The expressions "total" and "partial" anomalous correspondence used by Grant [106] in this sense are meaningless and should not be adopted.

VIII. CONCLUSIONS

An anomalous sensorial retinal relationship is found in a large number of cases of concomitant strabismus. It represents an adaptation of the sensorial apparatus of the eyes to their abnormal relative position. Its essence consists in the acquisition of more or less stable common visual directions between *de norma* disparate retinal elements. It is not a condition in which common visual directions are absent, as has been claimed.

This anomalous sensorial retinal relationship cannot be understood, nor can all the accompanying phenomena be explained, on the basis of the projection theory of spatial localization. Only the theory of the subjective visual directions, on the broad foundation of the methods of exact subjectivism, permits a satisfactory understanding of all pertinent phenomena. It must also be clearly recognized that the anomalous retinal relationship refers to the relative spatial localization. It must not be confused with anomalies in the absolute (egocentric) localization, such as occur in cases of recent paralyses of the ocular muscles.

Clinical observations on the group of patients with mixed correspondence in whom strabismus has existed since the earliest days of life clearly show that normal retinal correspondence is the result of an innate preformed mechanism.

Anomalous correspondence, on the other hand, is acquired through usage. It is closely connected with other sensorial phenomena in concomitant strabismus, such as regional inhibition. A number of conditions are required for its establishment; time, usage and individual adaptability are most important. The basic factor in the stability of the

106. Grant, H. W.: Some Observations on Divergent Strabismus with Anomalous Retinal Correspondence, Am. J. Ophth. **28**:472, 1945.

anomalous correspondence is the stability of the relative position of the eyes. The more stable the latter, the more stable is the anomalous sensorial retinal relationship.

The results obtained in the various types of tests devised for the determination of the sensorial retinal relationship in patients are a measure of this stability. The more deeply the anomalous correspondence is rooted, the more consistently will it be found to be present under all the different test conditions.

The therapy of anomalous correspondence, so essential for the functional cure of strabismus, presents a most difficult problem. Only a full grasp of the essence of the condition can make an evaluation of past achievements possible and insure progress in the future.

520 Commonwealth Avenue.

Clinical Notes

METHOD FOR THE MAINTENANCE OF STERILITY OF OPHTHALMIC SOLUTIONS

Gilbert N. Haffly, M.D., and Carl D. F. Jensen, M.D., Seattle

It is well known that the majority of ophthalmic surgeons are suspicious of the sterility of the ophthalmic solutions presented for use during the course of a surgical procedure on the eye and in the postoperative care. This skeptical attitude extends from the confines of the smallest community or private hospital to the marble halls of the greatest teaching institutions. It manifests itself by the dubious regard with which ophthalmic surgeons and surgical nurses view the varied assortment of dropper bottles present on the average eye-dressing tray. Praiseworthy attempts are regularly made to assure the sterility of such ophthalmic solutions by ordering frequent resterilization of those solutions commonly used in the surgical and postoperative surgical care of ophthalmic patients, particularly those who have undergone intraocular operations. However, from the moment a sterilized dropper bottle is opened its contents cease to be sterile.

Post [1] has pointed out that despite the fact that in recent years ophthalmic surgeons have conformed more closely to the concepts of asepsis existent in general surgery, such as the wearing of rubber gloves, the incidence of infection in ophthalmic surgery remains only slightly altered. He advanced the plea that ophthalmologists should search in every direction for any additional precaution that may prevent the tragedy of the postoperative infection.

Despite the well known fact that by no possible method can the conjunctiva be rendered completely sterile, no ophthalmic surgeon would care to feel guilty of introducing pathogenic organisms into the eye which has been operated on. The need for a simple and convenient method of maintaining the sterility of ophthalmic solutions is apparent.

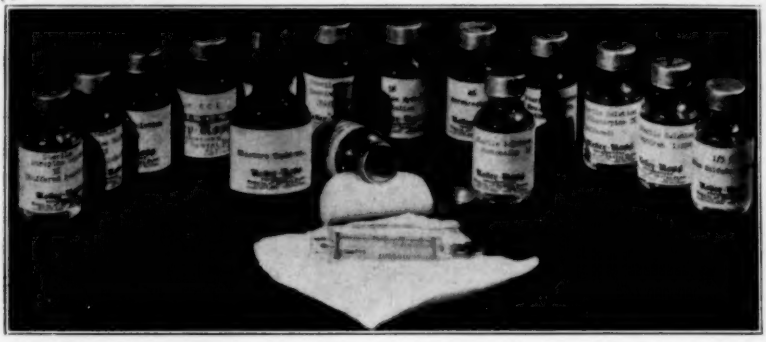
The picture presented is self explanatory. A sterilized cotton applicator is utilized to paint the rubber cork of the stoppered vial with tincture of zephiran chloride. The detergent and germicidal effects of this powerful drug are sufficient to render the corked surface of the vial sterile in a matter of several seconds. Since the picture exhibited was taken, a change of importance has been suggested. To prevent the possible careless introduction of zephiran chloride into the eye, however unlikely, the bottle of tincture of zephiran chloride should not be of the drop bottle type, but, rather, should be one with a simple screw-on cap. The sterile 2 cc. syringe and needle is utilized to withdraw the sterile contents of the solution desired. It has been found that by expressing the contents of the syringe through the tip of the hypodermic needle

1. Post, M. H., Jr.: Dust-Borne Infection in Ophthalmic Surgery, Tr. Am. Ophth. Soc. **43**:79, 1945.

the controlled formation of individual drops is assured. The vials may be resterilized at desired intervals. Since labels are frequently lost during the course of sterilization, the vials must be permanently marked appropriately to prevent any possible confusion as to the contents of each and every vial. A special heat-resistant ink is used for this purpose.

PHARMACOLOGIC PROCEDURE

The material is dissolved when indicated in acid buffer solution (boric acid, 12.4 Gm.; potassium chloride, 7.4 Gm.; distilled water, q. s. 1,000 cc.) and adjusted with alkaline buffer solution (sodium carbonate anhydrous, 21.2 Gm.; distilled water, q. s. 1,000 cc.) to the desired p_H according to Gifford's scale. Twenty cubic centimeter, rubber-capped vaccine vials, after thorough cleansing, are washed out with successive rinsings of filtered distilled water. The solution is then filtered into the vial through the same funnel and filter paper used in



Method of maintaining sterility of ophthalmic solutions.

the rinsings. This provides a well washed filter paper and eliminates all particles of paper or dust. The vial is then capped and autoclaved at 240 F. for twenty minutes.

NOTE.—A suitable eye-dressing tray of stainless steel that can be put in the autoclave with the vials in place is being made and will be the subject of a future article.

1315 Medical Dental Building (1)

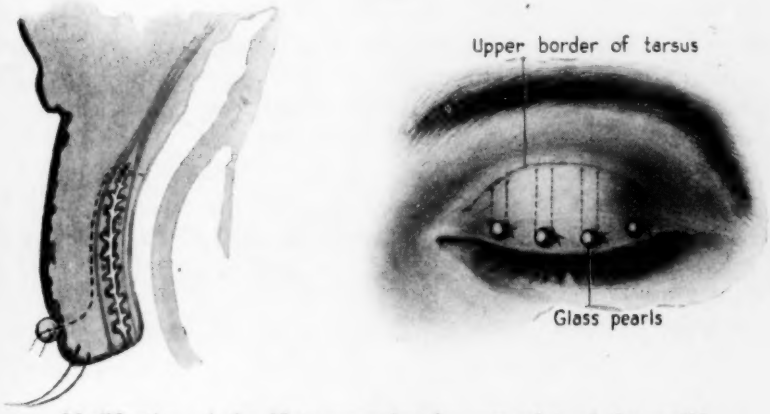
A SIMPLE MODIFICATION OF OPERATIONS FOR ENTROPION OF THE EYELIDS

RUDOLF H. BOCK, M.D., PEIPING, CHINA

Working in a country where trachoma is responsible for about one half of all the ophthalmic cases and where, therefore, operative procedures to correct entropion and trichiasis make up 30 to 40 per cent of all the operations, one tries to find simpler methods to substitute

for the complicated and time-consuming plastic procedures, such as the Hotz and Snellen operations.

The method described makes use of the principle of the Hotz operation, i. e., to fix the margin of the lid to the upper border of the tarsus by sutures. This, however, is done without cutting the skin, but only by passing three or four double-armed sutures from the conjunctival side through the upper border of the tarsus, then along the anterior surface of the tarsus downward and finally emerging through the skin 1 to 2 mm. above the row of eyelashes. The other end of the silk suture is passed in the same way about 2 mm. away from the first one, and the two are tied on the skin side over a glass pearl on a small gauze roll after exerting the necessary pull to produce the desired correction. There should be some overcorrection immediately after operation, as the sutures will always cut a little into the tissue later on. It is impor-



Modification of the Hotz operation for entropion of the eyelid.

tant that all the three or four pairs of sutures come out at exactly the same level. An intermarginal incision may or may not be performed. The stitches are left in position for eight to ten days. Special care should be taken on changing the dressing to avoid stitch infection.

The advantage of this procedure is its simplicity and the fact that it causes very little trauma. It will be indicated mainly in cases of relatively mild entropion, in which the tarsus is not much thickened or curved by scar tissue. Cases of severe entropion remain the domain of major operations which also correct the shape and position of the tarsus. Entropion of the lower lid can be corrected by the same method, but the effect will be not so great because of the narrowness of the tarsus of this lid. In cases with acute inflammation of the conjunctiva this method should not be used for fear of stitch infection from the conjunctival side. A spastic entropion may be operated on with good results by this method, which can be indicated as a cosmetic procedure only.

INSTRUMENTS FOR USE IN OPHTHALMIC SURGICAL PROCEDURES

Carl Apple, M.D., Chicago

CORNEAL SCISSORS

This instrument is a modification of the Walker scissors. The lower tip extends 1 mm. beyond the upper tip; the extended part is 1 mm. wide; the extreme end is rounded, and the surface is highly polished. This enables the operator to enter the anterior chamber with less difficulty and without trauma to the iris after the original section

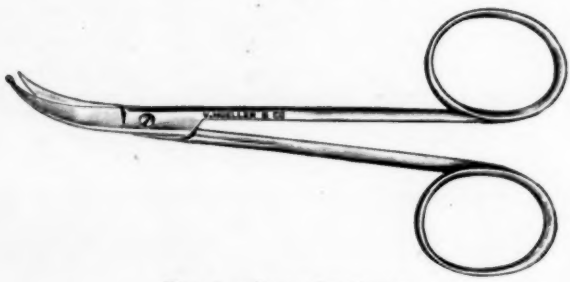


Fig. 1.—Corneal scissors.

of the cornea with a keratome, or whenever the corneal section has to be enlarged. This scissors should also be useful in removing strips of sclera in eye-shortening operations. I have used the scissors for several years and have found them very useful. Precaution must be taken to have them very sharp at all times.

IRIS REDEPOSITOR

My associates and I have used this iris redepositor at the Research Hospital of the University of Illinois for the past six years and have found it a valuable instrument. The handle may be rounded or square;

Fig. 2.—Iris redepositor.

the round handle enables the operator to rotate it between the thumb and the index finger. The redepositor portion is bent at an angle of 115 degrees and is 5 mm. long and 2 mm. wide; the extreme end is rounded and dull, and the surface is highly polished.

55 East Washington Street.

Ophthalmologic Reviews

HYPOVITAMINOSIS A IN OPHTHALMOLOGY

R. L. SCHMIDTKE, M.D.
ST. PAUL

INTRODUCTION

Purpose.—The signs and symptoms of gross vitamin A deficiency both in experimental animals and in human subjects are well known to all students of medicine and nutrition and will not be discussed in this paper. A satisfactory presentation of the accepted clinical manifestations of vitamin A deficiencies may be found in Duke-Elder's "Text-Book of Ophthalmology." In reviewing the literature with reference to vitamin A deficiency, it has been my aim to correlate the thoughts and experiences of the various authors, so that a better clinical application of the known facts may be made.

Nomenclature.—The term "hypovitaminosis" has been chosen because the word "avitaminosis" carries a meaning of complete absence of the vitamin under consideration. Such a condition is difficult to attain experimentally if the animal is provided with an adequate diet except for the vitamin under observation and probably never exists so far as the human case of vitamin deficiency is concerned.

Vitamins in General.—Vitamins, important as they are for the maintenance of health and well-being, have been taken over by the makers of "patent remedies" and are being sold to the general public under a variety of attention-compelling names and without the physician's advice or prescription. Vitamins lend themselves well to this type of exploitation of the public because their toxicity is low and their importance to general health cannot be denied. It is for this reason, I believe, that conservative medical men try to avoid the diagnosis of "hypovitaminosis" as often as possible, especially in this country, because Americans as a group are better fed than any other people in the world. Nevertheless, I feel that Duke-Elder [1] presented the case of vitamin deficiency well when he stated:

Thesis submitted to the Graduate Faculty of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Ophthalmology, June 1946.

1. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2, p. 1424.

Although the deficiency diseases are dramatic and interest-compelling clinical entities, it is probable that the greatest importance of vitamin deficiency in clinical medicine lies in borderline cases of ill health which frequently puzzle the physician and disable the patient. It is quite possible that in partial avitaminosis the cumulative damage to the important epithelial structures of the eye—the cornea, the lens, and the retina—may lower their vitality, favor the incidence and prolong the activity of infections and precipitate degenerative changes on a wider scale than is yet realized. Nor should their therapeutic application be limited to the treatment of frank evidences of deficiency.

Vitamin A.—Sometimes referred to as the ophthalmic vitamin,[2] vitamin A was the first of these important dietary factors to be discovered by McCollum and Davis.[3] That xerophthalmia, keratomalacia and night blindness are the ocular signs and symptoms of hypovitaminosis A has been established by numerous animal experiments, foremost of which are the work of Mori,[4] Yudkin,[5] Gudjonsson[6] and Johnson[7]; the studies of Blegvad[8] and his conclusion that xerophthalmia, keratomalacia and xerosis conjunctiva in Denmark during the period 1909 to 1920 was a vitamin A deficiency; the extensive observations of Pillat[9] on effects of vitamin A deficiency in China, and the studies on

2. Jackson, E.: The Ophthalmic Vitamin, editorial, Am. J. Ophth. **18**:967, 1935. Duke-Elder,[1] p. 1423.

3. McCollum, E. V., and Davis, M.: Observations on the Isolation of the Substance in Butter Which Exerts a Stimulating Influence on Growth, J. Biol. Chem. **19**:245, 1914.

4. Mori, S.: Primary Changes in Eyes of Rats Which Result from Deficiency of Fat-Soluble A in Diet, J. A. M. A. **79**:197 (July 15) 1922.

5. Yudkin, A. M.: (*a*) Ocular Manifestations of Rats Which Result from Deficiency of Vitamin A in Diet, J. A. M. A. **79**:2206 (Dec. 30) 1922; (*b*) Ocular Disturbances Produced in Experimental Animals by Dietary Changes: Clinical Implications, ibid. **101**:921 (Sept. 16) 1933; (*c*) Clinical Implications of Ocular Disturbances Produced in Experimental Animals by Dietary Changes, Tr. Sect. Ophth., A. M. A., 1933, p. 27; Arch. Ophth. **11**:902 (May) 1934. (*d*) Yudkin, A. M.; Orten, M. S., and Smith, A. H.: The Production and Cure of Ocular Disturbances in Adult Albino Rats by Adjustment of Vitamin A: Clinical Implications, Am. J. Ophth. **20**:1115, 1937.

6. Gudjonsson, S. V.: Xerophthalmia in Rats and Periocular Reaction, Acta ophth. **8**:184, 1930.

7. Johnson, M. L.: Degeneration and Repair of the Rat Retina in Avitaminosis A, Arch. Ophth. **29**:793 (May) 1943.

8. Blegvad, O.: Xerophthalmia, Keratomalacia, and Xerosis Conjunctivae, Am. J. Ophth. **7**:89, 1924.

9. Pillat, A.: (*a*) Frequency of Deficiency Diseases of the Eye Due to Lack of Vitamin A in a Military Camp North of Peiping, Nat. M. J. China **15**:585, 1929; (*b*) Main Symptoms of the Eye in Vitamin A Deficiency in Adults, ibid. **15**:614, 1929; (*c*) Prexerosis and Xerosis of the Cornea as Independent Disease Pictures of Eye in Deficiency Disturbances of Adults, Arch. f. Ophth. **124**:486, 1930; (*d*) The Classical Symptom Complex of Vitamin A Deficiency, Wien. klin. Wchnschr. **53**:779, 1940.

experimentally induced vitamin A deficiency in human volunteers by Mandelbaum and Hecht,[10] Steffen, Bair and Sheard[11] and others. Vail,[12] in his editorial on vitamin therapy in ophthalmology, stated:

> It is but natural that in the enthusiastic reception of this knowledge, abuses should have crept in. If the history of any drug or healing agent be investigated, this same abuse at the onset of its application will be found. A search of the medical literature of the past will disclose serious articles in first-rate journals by outstanding men, devoted to astonishing reports of successful therapeutic results, in all sorts of conditions.

Patients with ocular diseases, the treatment of which has baffled the ophthalmologist in the past, are now being enthusiastically dosed with one or more of the vitamins, sometimes without any apparent logic. Vitamin A has been prescribed and reported on in the treatment of such varying conditions as tuberculous diseases of the eye,[13] phlyctenular conjunctivitis,[14] follicular conjunctivitis,[15] keratoconjunctivitis sicca,[16] keratitis superficialis,[17] asthenopia,[18] myopia[19] and trachoma,[20] while

10. Mandelbaum, J., and Hecht, S.: Dark Adaptation Under Controlled Dietary Vitamin A Conditions, Am. J. Physiol. **129**:416, 1940; Dark Adaptation and Experimental Human Vitamin A Deficiency, ibid. **130**:651, 1940.

11. Steffen, L. F.; Bair, H. L., and Sheard, C.: Dark Adaptation and Dietary Deficiency in Vitamin A, Am. J. Ophth. **23**:1325, 1940.

12. Vail, D.: Vitamin Therapy in Ophthalmology, editorial, Am. J. Ophth. **24**:1325, 1941.

13. Sal Lence: Vitamin Therapy in Ophthalmology, Arch. de oftal. hispano-am. **31**:386, 1931. Fronimopoulos, J.: What Influence Has Vitamin A Deficiency on the Development of the Relapsing Seasonal Disease, Allergic (Scrofulous) Keratoconjunctivitis? Klin. Monatsbl. f. Augenh. **104**:1, 1940; A and C Hypovitaminosis in Case of Tuberculous Disease of the Eye, ibid. **105**:707, 1940.

14. Tai, M. C.: Hypodermic Injections of Carotene in Treatment of Phlyctenular Conditions and Vitamin A Deficiency Diseases in Ophthalmology, Chinese M. J. **50**:1453, 1936.

15. Sandels, M. R.; Cate, H. D., and Wilkinson, K. P.: Follicular Conjunctivitis in School Children's Expression of Vitamin A Deficiency, Am. J. Dis. Child. **62**:101 (July) 1941.

16. (*a*) Grósz, S.: Etiology and Treatment of Keratoconjunctivitis Sicca, Klin. Monatsbl. f. Augenh. **97**:472, 1936. (*b*) Gifford, S. R.: Vitamin Therapy in Ocular Conditions, Arch. Ophth. **30**:162 (July) 1943. (*c*) Gifford, S. R.; Puntenney, I., and Bellows, J.: Keratoconjunctivitis Sicca, ibid. **30**:207 (Aug.) 1943.

17. Stocker, F.: Keratitis Superficialis and Vitamin A, Schweiz. med. Wchnschr. **66**:335, 1936.

18. Cordes, F. C., and Harrington, D. O.: Asthenopia Due to Vitamin A Deficiency, Am. J. Ophth. **22**:1343, 1939. Newton, F. H., and Schade, A. H.: An Experiment to Determine the Conservation of Vitamin A in the Eye Under Strain, Ohio State M. J. **39**:827, 1939. Pett, L. B.: Riboflavin and Vitamin A in Relation to "Eyestrain," Canad. M. A. J. **49**:293, 1943.

Levine [21] and Casini [22] expressed the belief that a vitamin A deficiency may be the underlying cause of retinitis pigmentosa and Dor [23] stated the opinion that insufficiency of vitamin A might be a factor in the development of strabismus when there is a hereditary predisposition. Keratoconus has been experimentally produced in rats by Mutch and Richards,[24] while Hale [25] produced anophthalmos in pigs and Warkany and Schraffenberger [26] induced congenital malformations in rats through vitamin A deficiency in the mothers. From the foregoing evidence, it is obvious that there are "tares among the wheat." Again, quoting from Vail's [12] editorial:

> The only way in which our prejudices can be debunked is by the publication of articles by competent and trustworthy observers who have access to a large amount of clinical and experimental facilities. The question, "Is this honest work?" must be constantly posed. Subtle influences such as the desire to satisfy enthusiastic ambition, or to promote the interests of pharmaceutical benefactors must be searched for and weighed in the balance by the reader. The logic of the drug action must be apparent to some extent at any rate. Finally, the test of one's own experience must be made and impressions turned into facts by observation.

NIGHT BLINDNESS AND DARK ADAPTATION

Nomenclature.—According to Dorland,[27] the term "nyctalopia" is derived from the Greek words meaning "night-blind eye," while the term "hemeralopia" is derived from the Greek words meaning "day-blind eye." Since each term has been used in the literature to mean both night and day blindness, the term "night blindness" will be used in this paper to avoid confusion. Many of the authors cited here, however, have used the word "hemeralopia" to designate "night blindness."

Vitamin A and Night Blindness.—That a lack of vitamin A in the diet will cause functional night blindness has been definitely established by

19. Laval, J.: Relationship Between Myopia and Avitiminosis, Am. J. Ophth. **24**:408, 1941. Guha, G. S.: The Role of Vitamins in Ocular Affections, Proc. All-India Ophth. Soc. **4**:82, 1935.

20. Kendall, A. I., and Gifford, S. R.: Trachoma and Avitaminosis, Arch. Ophth. **4**:322 (Sept.) 1930.

21. Levine, J.: Is Retinitis Pigmentosa Due to Vitamin Deficiency? Arch. Ophth. **9**:453 (March) 1933.

22. Casini, F.: Retinitis Pigmentosa and Avitaminosis, Arch. di ottal. **42**: 409, 1935.

23. Dor, L.: Strabismus and Avitaminosis, Arch. d'opht. **50**:667, 1933.

24. Mutch, J. R., and Richards, M. B.: Keratoconus Experimentally Produced in Rat by Vitamin A Deficiency, Brit. J. Ophth. **23**:381, 1939.

25. Hale, F.: The Relation of Vitamin A to Anophthalmos in Pigs, Am. J. Ophth. **18**:1087, 1935.

26. Warkany, J., and Schraffenberger, E.: Congenital Malformations Induced in Rats by Maternal Vitamin A Deficiency, Arch. Ophth. **35**:150 (Feb.) 1946.

27. Dorland, W. A.: The American Illustrated Medical Dictionary, Philadelphia, W. B. Saunders Company, 1938.

the studies, observations and experiments of such men as Fridericia and Holm,[28] Holm,[29] Yudkin,[5c] Pillat [9a,b,d] and Aykroyd,[30] and Eusterman and Wilbur [31] quoted Hippocrates as advocating the use of an abundance of liver and honey in cases of night blindness. However, as has been pointed out by Feldman [32] and Manville,[33] not all cases of night blindness are due to vitamin A deficiency. Certain organic diseases, such as glaucoma, choroiditis, optic neuritis, retinitis pigmentosa and retinal detachment, have some degree of night blindness as one of the symptoms; but, as pointed out in Post's [34] editorial on vitamin A deficiency, it would not be illogical to assume that in these diseases in which night blindness is an important symptom a vitamin A deficiency might be suspected as an etiologic factor. The night blindness associated with the aforenamed ocular diseases has been referred to only in order more nearly to complete the picture. It is my opinion, based on my review of the literature, that few, if any, of these conditions have vitamin A deficiency as an underlying cause.

Night Blindness and Dark Adaptation.—Most investigators seem to take for granted that night blindness and poor dark adaptation are synonymous. Yudkin [35] warned that ". . . It is important to decide whether hemeralopia and poor dark adaptation are synonymous, for at present investigators are classifying poor dark adaptation as hemeralopia, and some have gone still further and assumed that poor dark adaptation or hemeralopia is a sign of vitamin A deficiency. I cannot fully subscribe to the latter assumption until further investigation is made," while Woisika [36] stated that ". . . In the present state of knowledge of scotopic vision, the term 'night blindness' and 'poor dark adaptation' should not be used synonymously as to tests."

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28. Fridericia, L. S., and Holm, E.: Experimental Contributions to the Study of the Relation Between Night Blindness and Malnutrition, Am. J. Physiol. **73**:63, 1925.

29. Holm, E.: Demonstration of Hemeralopia in Rats Nourished on Food Devoid of Fat-Soluble A Vitamin, Am. J. Physiol. **73**:79, 1925.

30. Aykroyd, W. R.: Night Blindness Due to Vitamin Deficiency, Tr. Ophth. Soc. U. Kingdom **50**:230, 1930.

31. Eusterman, G. B., and Wilbur, D. R.: Clinical Features of Vitamin A Deficiency, J. A. M. A. **98**:2054 (June 11) 1932.

32. Feldman, J. B.: Dark Adaptation, Night Blindness, and Glaucoma, Arch. Ophth. **22**:595 (Oct.) 1939.

33. Manville, I. A.: Nutrition and Night Blindness, Northwest Med. **38**: 208, 1939.

34. Post, L. T.: Vitamin A Deficiency, editorial, Am. J. Ophth. **19**:617, 1936.

35. Yudkin, A. M.: Vitamins in Treatment and Prevention of Ocular Diseases, Arch. Ophth. **19**:366 (March) 1938.

36. Woisika, P. H.: An Evaluation of the Dark Test, Ann. Int. Med. **21**:101 1944.

Dark Adaptation.—Dark adaptation is the ability of the eye to adjust from illumination of high intensity to that of low intensity so that better visual acuity can be attained. Since, as previously stated, functional night blindness is due to a vitamin A deficiency, it seemed only reasonable that attempts to measure dark adaptation should be made and these results used as a test for vitamin A deficiency. Hecht and Mandelbaum [37] argued thus:

> After the establishment of vitamin A as a factor in the visual cycle, it seemed logical to use the properties of vision for the detection of early stages in vitamin A deprivation.

Hecht [38] stated:

> Dark adaptation is an expression of the accumulation in the eye of photosensitive substances, such as visual purple in the rods and visual violet in the cones. This accumulation of sensitive materials is determined among other things by the vitamin A content of the diet, since night blindness due to dietary deficiency has been cured by the addition of vitamin A to an inadequate diet.

In an attempt to correlate poor dark adaptation and vitamin A deficiency, numerous investigations were undertaken. Frandsen,[39] using dark adaptation as a test for mild degrees of vitamin A deficiency, reported that after administration of vitamin A and calcium to 23 patients for one month 11 showed normal dark adaptation. Similar results were reported by Jeans and Zentmire [40]; Jeans, Blanchard and associates,[41] and Caussade, Thomas, Neimann and Davidsohn,[42] while Jeghers,[43] Mathis [44] and Blanchard and Harper [45] found a definite relationship

37. Hecht, S., and Mandelbaum, J.: Relation Between Vitamin A and Dark Adaptation, J. A. M. A. **112**:1910 (May 13) 1939.

38. Hecht, S.: Vitamin A and Vision, Arch. Ophth. **23**:874 (April) 1940.

39. Frandsen, H.: Determination of Hemeralopia as a Test for Mild Degrees of Vitamin A Deficiency, Hospitalstid. (med. selsk. forh.) **77**:42-48, 1934.

40. Jeans, P. C., and Zentmire, Z.: (*a*) A Clinical Method for Determining Moderate Degrees of Vitamin A Deficiency, J. A. M. A. **102**:892 (March 24) 1934; (*b*) The Prevalence of Vitamin A Deficiency Among Iowa School Children, ibid. **106**:996 (March 21) 1936.

41. Jeans, P. C.; Blanchard, E. L., and Zentmire, Z.: Dark Adaptation and Vitamin A, J. A. M. A. **108**:451 (Feb. 6) 1937. Jeans, P. C.; Blanchard, E. L., and Satterthwaite, F. E.: Dark Adaptation and Vitamin A: Further Studies with Biophotometer, J. Pediat. **18**:170, 1941.

42. Caussade, L.; Thomas, C.; Neimann, N., and Davidsohn, S.: Utilization of the Hemeralopia Test for Detection of Vitamin A Deficiency in Children, Bull. Soc. d'opht. de Paris **50**:415, 1938.

43. Jeghers, H.: The Degree and Prevalence of Vitamin A Deficiency in Adults, J. A. M. A. **109**:756 (Sept. 18) 1937.

44. Mathis, G.: Avitaminosis A and Hemeralopia, Rassegna ital. d'ottal. **8**: 353, 1939.

45. Blanchard, E. L., and Harper, H. A.: Measurement of Vitamin A Status of Young Adults by the Dark-Adaptation Technique, Arch. Int. Med. **66**:661 (Sept.) 1940.

between vitamin A–deficient diet and poor dark adaptation. Attacking the problem from another angle, Krakov and Semenovskaja [46] studied the dark adaptation of a patient being treated for cystitis who received no food, and only water, for fifty days. On the forty-fifth day he showed severe night blindness ("hemeralopia"), according to the authors, while two weeks after being on a regular diet the dark adaptation was well within normal limits. Wald, Jeghers and Arminio [47]; Caussade, Thomas, Neimann and Davidsohn [48] and Mandelbaum and Hecht [10] placed human subjects on vitamin A–deficient diets to study the effect of such diets on dark adaptation, and they came to the conclusion that vitamin A deficiency results in poor dark adaptation. Convincing as these reports may seem, there is much evidence to show that dark adaptation is not a test of vitamin A deficiency. Tansley,[49] after reviewing the literature up to 1939, expressed great doubt whether dark adaptation curves, as they are usually made, are of any value in detecting slight degrees of malnutrition due to vitamin A deficiency. Nagy and Incze,[50] following the procedure of Jeans and Zentmire,[40a] examined a series of children in two different schools who were known to receive diets low in vitamin A, and the children in a third school, whose diets were adequate were used as a control. The authors concluded that no differences in dark adaptation could be observed in children who varied widely in their vitamin consumption, while Isaacs, Jung and Ivy [51] found no correlation between dark adaptation and the vitamin A intake of a group of healthy medical students. Since the time of Tansley's [49] conclusions, in 1939, numerous more carefully controlled investigations have been carried on by Thompson, Griffith, Mutch, Lubbock, Owen and Logaras [52]; Steffen, Bair and Sheard [11]; Isaacs, Jung and Ivy [53]; Stewart [54]; Dann

46. Krakov, S. W., and Semenovskaja, E. N.: The Influence of Starvation on Visual Function, Arch. f. Ophth. **132**:370, 1934.

47. Wald, G.; Jeghers, H., and Arminio, J.: An Experiment in Human Dietary Night Blindness, Am. J. Physiol. **123**:732, 1938.

48. Caussade, L.; Thomas, C.; Neimann, N., and Davidsohn, S.: Hemeralopia in Induced Hypovitaminosis A, Bull. Soc. d'opht. de Paris **50**:276, 1938.

49. Tansley, K.: Night Blindness, Brit. J. Ophth. **23**:161, 1939.

50. Nagy, M., and Incze, K.: Relation of Hypovitaminosis to Dark Adaptation, Arch. f. Augenh. **109**:567, 1936.

51. Isaacs, B. L.; Jung, F. T., and Ivy, A. C.: Vitamin A Deficiency and Dark Adaptation, J. A. M. A. **111**:777 (Aug. 27) 1938.

52. Thompson, A. M.; Griffith, H. D.; Mutch, J. R.; Lubbock, D. M.; Owen, E. C., and Logaras, G.: A Study of Diet in Relation to Health, Brit. J. Ophth. **23**:697, 1939.

53. Isaacs, B. L.; Jung, F. T., and Ivy, A. D.: Clinical Studies of Vitamin A Deficiency: Biophotometer and Adaptometer (Hecht) Studies on Normal Adults and on Persons in Whom an Attempt Was Made to Produce Vitamin A Deficiency, Arch. Ophth. **24**:698 (Oct.); correction, ibid. **25**:158 (Jan.) 1941.

54. Stewart, C. P.: Nutritional Factors in Dark Adaptation, Edinburgh M. J. **48**:217, 1941.

and Yarbrough [55]; Dow and Steven [56]; Oldham, Roberts, McLennan and Schultz,[57] and Pollack.[58] Thompson and associates [52] came to the conclusion:

> It would appear from our results that neither rate of dark adaptation nor light threshold of the fully dark adapted eye has necessarily a close correlation with intake of vitamin A in the diet. Considerable variation may occur in one individual and between individuals on the same diet.

Dann and Yarbrough's [55] 2 subjects failed to show night blindness measurable by the dark adaptometer of Hecht and Shlaer after five weeks on a diet deficient in vitamin A. Isaacs and her co-workers [53] placed one group of normal adults on large daily doses of liquid petrolatum in an attempt to remove the fat-soluable vitamin A from the food and expel it with the feces. No significant changes in the dark adaptation of this group as compared with that of a control group were found. These investigators then placed 3 subjects on a very low vitamin A diet and found that "a diet containing an average of 74 U. S. P. units of vitamin A daily failed to produce measurable visual evidence or subjective signs of deficiency in 3 subjects maintained on the diet for forty-three to forty-nine days," while 300,000 units of vitamin A daily failed to improve the dark adaptation in some patients suspected of having a vitamin A deficiency. That the adaptometer designed by Hecht and Shlaer is a more reliable instrument for testing dark adaptation than the biophotometer is now generally accepted. Using this newer instrument, Oldham and associates [57] repeated the work of Jeans and Zentmire [40a] among school children and came to the same conclusion as did Nagy and Incze,[50] namely, that there was no correlation between adaptometer readings and the daily vitamin A intake. A number of investigators have shown that many factors other than vitamin A can influence dark adaptation. Stewart [54] pointed out that fatigue and lack of sleep have an adverse effect on dark adaptation; so also does old age. Pollack,[58] studying dark adaptation in patients with peptic ulcer, showed that the degree of abnormality bore some relation to deterioration in general condition, while McDonald and Adler [59] have shown that anoxemia

55. Dann, W. J., and Yarbrough, M. E.: Dark Adaptometer Readings of Subjects on a Diet Deficient in Vitamin A, Arch. Ophth. **25**:833 (May) 1941.

56. Dow, D. J., and Steven, D. M.: Investigation of Simple Methods for Diagnosing Vitamin A Deficiency by Measurements of Dark Adaptation, J. Physiol. **100**:256, 1941.

57. Oldham, H.; Roberts, L. J.; McLennan, K., and Schultz, F. W.: Dark Adaptation of Children in Relation to Dietary Levels of Vitamin A, J. Pediat. **20**:740, 1942.

58. Pollack, H.: Metabolic and Nutritional Factors Affecting Dark Adaptation in Peptic Ulcer Patients, Tr. Ophth. Soc. U. Kingdom **63**:69, 1943.

59. McDonald, R., and Adler, F. H.: (*a*) Effect of Anoxemia on the Dark Adaptation of the Normal and of the Vitamin A–Deficient Subject, Arch. Ophth.

affects the dark adaptation curve. The truth is that most investigators have lost sight of the fact that tests for dark adaptation are, by their very nature, subjective. The only references to this fact were made by McDonald and Adler [59a] and by Riddell.[60]

Vitamin A Content of the Blood.—It followed naturally that when the biochemist developed methods for determining the vitamin A content of the blood this laboratory procedure should be applied to cases of suspected vitamin A deficiency and the results correlated with dark adaptation. Caveness, Satterfield and Dann [61] found only a slight correlation between biophotometer readings and the vitamin A level of the blood, while Bodansky, Lewis and Haig [62] showed a direct relationship between the vitamin A level of the plasma and vitamin A consumption in infants. By using a special technic for dark adaptation, they concluded that the vitamin A level of the plasma is a considerably more sensitive indicator of vitamin A deficiency than is dark adaptation. "The determination of the level of vitamin A in the blood," stated Goldberg and Schlivek,[63] "provides an objective laboratory method of determining whether vitamin A deficiency is present." The work of Haig and Patek [64] and the results of Steven [65] also confirmed the earlier reports that no correlation is apparent between dark adaptation and the vitamin A level of the plasma.

Other Tests Closely Related to Dark Adaptation.—In 1932 Kiang [66] reported his observations on the visual fields in patients with various forms of vitamin A deficiency. He studied the blue, red and white fields but could find no definite correlation between the clinical symptoms and the relation of the color fields one to another. However, he concluded that on the whole the contraction, especially of the blue field, is pro-

22:980 (Dec.) 1939; (b) Clinical Evaluation of Tests of Dark Adaptation, ibid. **24**:447 (Sept.) 1940; correction, ibid. **24**:1258 (Dec.) 1940.

60. Riddell, W. J. B.: Scientific and Clinical Aspects of Night Vision, Tr. Ophth. Soc. U. Kingdom **63**:43, 1943.

61. Caveness, H. L.; Satterfield, G. H., and Dann, W. J.: Correlation of the Results of the Biophotometer Test with Vitamin A Content of Human Blood, Arch. Ophth. **25**:827 (May) 1941.

62. Bodansky, O.; Lewis, J. M., and Haig, C.: Comparative Value of Blood Plasma Vitamin A Concentration and Dark Adaptation as a Criterion of Vitamin A Deficiency, Science, **94**:370, 1941.

63. Goldberg, H. K., and Schlivek, K.: Necrosis of the Cornea Due to Vitamin A Deficiency: Report of a Case, Arch. Ophth. **25**:122 (Jan.) 1941.

64. Haig, C., and Patek, A. J., Jr.: Vitamin A Deficiency in Laennnec's Cirrhosis, J. Clin. Investigation **21**:309, 1942; Relation Between Dark Adaptation and the Level of Vitamin A in the Blood, ibid. **21**:377, 1942.

65. Steven, D. M.: Experimental Human Vitamin A Deficiency, Tr. Ophth. Soc. U. Kingdom **62**:259, 1942.

66. Kiang, S. M.: Observation on the Visual Fields in Various Forms of Vitamin A Deficiency, Nat. M. J. China **18**:827, 1932.

portional to the other symptoms. Nearly ten years later Rauh [67] showed that a narrowing of the color field for yellow paralleled the degree of night blindness and in severe cases the field for yellow lay within or crossed the border of the field for green; in 1944 Hamilton, Briggs and Butler [68] reported a case of partial red-green blindness in which the condition became normal after administration of large doses of vitamin A, only to lapse back to partial red-green blindness when the amount in the blood returned to its original level. Before any of these changes can be accepted as presumptive tests for vitamin A deficiency, many more investigations will have to be made and reported on.

CONJUNCTIVAL MANIFESTATIONS

Biomicroscopy.—That the slit lamp and the biomicroscope should be used as a part of the examination when vitamin A deficiency is suspected is self evident, but what changes in the ocular tissues can be accepted as early signs and symptoms of vitamin A deficiency is questionable. In 1941 Kruse,[69] after having conducted a survey on persons in a low income group, recommended the biomicroscopic examination as a simple, convenient, objective method of detecting early vitamin A deficiency. Berliner,[70] however, stated the opinion that many of the changes noted by Kruse are common presenile and senile changes, and not signs and symptoms of vitamin A deficiency. Only when more of the early ocular changes noted in cases of vitamin A deficiency are reported on will it be possible to draw definite conclusions.

Conjunctival Pigmentation.—In 1931 Pillat [71] reported on a peculiar pigmentation of the conjunctiva produced among Chinese as a result of vitamin A deficiency. The following year similar observations among Japanese who were subsisting on a vitamin A–deficient diet were reported by Matsuoka.[72] He expressed the belief that this pigmentation is an early sign of vitamin A deficiency. Whether such pigmentation of the conjunctiva occurs among less darkly pigmented races is doubtful.

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67. Rauh, W.: The Color Field in Experimental Night Blindness, Arch. f. Ophth. **141**:545, 1940.

68. Hamilton, W. F.; Briggs, A. P., and Butler, R. E.: The Testing of Color Vision in Relation to Vitamin A Administration, Am. J. Physiol. **140**:578, 1944.

69. Kruse, H. D.: The Ocular Manifestations of Avitaminosis A, with Especial Consideration of Detection of Early Changes by Biomicroscopy, Pub. Health Rep. **56**:1301, 1941; Milbank Mem. Fund Quart. **19**:207, 1941.

70. Berliner, M. L.: Early Detection of Avitaminosis A by Gross or Biomicroscopic Examination of Conjunctiva, Am. J. Ophth. **25**:302, 1942.

71. Pillat, A.: A Peculiar Form of Pigmentation of Conjunctiva in Disease Produced by Vitamin A Deficiency in Adults, Arch. f. Ophth. **127**:575, 1931.

72. Matsuoka, H.: Histologic Studies on Melanin Pigment in the Conjunctiva: II. Pigmentation of the Conjunctiva Following Diseases of Vitamin A Defect, Acta Jap. ophth. soc. **36**:131, 1932.

Other Conjunctival Changes.—For the accepted conjunctival signs and symptoms of vitamin A deficiency, the reader is again referred to Duke-Elder's [1] "Text-Book of Ophthalmology."

Pathogenesis.—The mechanism by which vitamin A deficiency is manifested by the epithelium of the cornea and conjunctiva is not known. Some of the theories are indicated here.

1. Desiccation following loss of lacrimation. This theory does not hold, because xerophthalmia may occur with persistence of lacrimation.

2. Lack of mucus due to atrophy of the goblet cells in the conjunctival epithelium. This theory has no more to offer than the first.

3. Loss of lysozyme in the tears as a result of vitamin A deficiency (Anderson[73]). The validity of this theory is questionable, because bacterial invasion is not a primary occurrence in xerophthalmia.

4. A neurotrophic disturbance. This theory is more satisfactory in explaining the corneal and conjunctival changes than any of the others. In testing the corneal sensibility in cases of vitamin A deficiency John [74] observed that as the disease advanced to the stage of prexerosis and xerosis the sensibility of the cornea might sink to one hundredth of the normal, while Mellanby [75] noted degenerative changes in the myelin sheath of the trigeminal nerve in experimentally induced vitamin A deficiency in animals.

KERATOCONJUNCTIVITIS SICCA

Occurrence.—Keratoconjunctivitis sicca is a relatively rare condition, found most frequently in women at the time of the menopause.

Symptoms.—The subjective symptoms are those of chronic conjunctivitis, severe photophobia, absence of lacrimal secretion and impaired vision. For a complete account of the symptoms, the reader is referred to Sjögren's [76] monograph on keratoconjunctivitis sicca. The interesting feature of this condition is that it has much in common with xerophthalmia.

Etiologic Factors.—Keratoconjunctivitis sicca is generally accepted as a partial symptom of a major syndrome due to a general hypofunction of the glands of internal secretion as a result of the menopause. It is of interest to note that at first Sjögren [77] felt that he was dealing

73. Anderson, O.: Lysozyme in Xerophthalmia, Hospitalstid. **75**:1029, 1932.

74. John, I.: Disturbance of Sensibility of Cornea and Conjunctiva in Xerosis and Keratomalacia of Adults, Arch. Ophth. **5**:374 (March) 1931.

75. Mellanby, E.: Xerophthalmia, Trigeminal Degeneration, and Vitamin A Deficiency, J. Path. & Bact. **38**:391, 1934.

76. Sjögren, H.: Keratoconjunctivitis Sicca, Acta ophth., 1933, supp. 2.

77. Sjögren, H.: Keratoconjunctivitis Sicca: Partial Symptom of a Major Syndrome, Arch. Ophth. **18**:675 (Oct.) 1937; On Keratoconjunctivitis Sicca, Acta ophth. **16**:70, 1938.

with some form of chronic infection; but after further microscopic studies of the lacrimal gland in the initial stage of the disease, he came to the conclusion that the primary and characteristic change in the syndrome is indicative not of a bacterial invasion but rather of a degeneration. In the meantime, Grósz [16] and Lisch [78] suggested that keratoconjunctivitis sicca might be due to a vitamin deficiency. Gifford [16b] and Gifford, Puntenney and Bellows,[16c] although not certain that keratoconjunctivitis sicca is due to vitamin A deficiency, stated that they always prescribed vitamin A for their patients with this condition.

CONGENITAL ANOMALIES

Animal Experiments.—In 1935 Hale [25] reported his results on the relationship of vitamin A to anophthalmos in pigs.

> These studies leave no reasonable doubt that a maternal deficiency of vitamin A will result in a variety of defects in the offspring, including blindness and even a failure of complete development of eye tissues, cleft palates, hare lip, and the arrested ascension of the embryo kidney. The question at once arises as to the relation of these results to various eye defects and weaknesses in the human race. It may be argued that there is a vast gap between pigs and people, but from the biological and nutritional standpoint, the differences are not so great as might appear at first glance. Both are omnivorus mammals with a long gestation period.

It is interesting to note that Warkany and Schraffenberger [79] produced much the same results in the offspring of rats kept on a diet low in vitamin A.

Human Cases.—How frequently vitamin A deficiency will cause ocular congenital anomalies is unknown at the time of this writing. No doubt a study of the problem in those parts of the world where starvation is a commonplace as a result of World War II would produce interesting results.

THERAPY

In the discussions up to this point, I have been concerned with the effects of vitamin A deficiency, and perhaps the impression has been given that deficiency results only from a reduced consumption of vitamin A. It will be wise to consider the other causes of vitamin A deficiency, in order to arrive at a more logical method of treatment.

Reduced Consumption.—That a reduced intake of vitamin A if continued over an extended period will result in a deficiency state is general knowledge and needs no further discussion.

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78. Lisch, K.: Heredity of Sjögren's Disease Associated with Keratoconjunctivitis Sicca, Arch. f. Augenh. **110**:357, 1937.

79. Warkany, J., and Schraffenberger, E.: Congenital Malformations of Eyes Induced in Rats by Maternal Vitamin A Deficiency, Proc. Soc. Exper. Biol. & Med. **57**:49, 1944.

Defective Absorption.—It is obvious that unless the vitamin A consumed is absorbed from the gastrointestinal tract a deficiency state may develop in spite of an adequate diet. Riddell [80] called attention to this in 1933. He found that definite vitamin A deficiency developed in a case of celiac disease because the patient was unable to absorb the fatty foods, which contained ample vitamin A. Prompt recovery followed when vegetables containing vitamin A were given in amounts sufficient to supply the necessary quantity of this vitamin. Similar results were reported by Wilbur and Eusterman,[81] in whose case vitamin A deficiency developed as a postoperative complication following operation on the gastrointestinal tract, and by Gamble,[82] in a case of cystic fibrosis of the pancreas.

Uneconomical Utilization.—All observers are aware that some internal combustion engines run more economically than others of the same general type, and every horseman will attest to the fact that some animals are much more economical to keep than others. This no doubt also holds true for the human being. That hepatic function may be one of the factors in vitamin A economy is understandable, because the liver, besides being the storehouse for this vitamin, is the organ for converting carotene into vitamin A. This has been pointed out by many observers, among whom are Jeghers,[83] Appelmans,[84] Wolff,[85] Patek and Haig [86] and Wohl and Feldman.[87]

Excessive Utilization During Rapid Growth.—Since it is generally known that a growing animal, including the human, requires more of all the food elements, namely, proteins, carbohydrates, fats, minerals and vitamins, per unit of body weight than the adult, it will not be necessary to discuss this phase of the problem further.

Excessive Utilization During Severe Illnesses.—Any condition which increases the general body metabolism, such as the infectious dis-

80. Riddell, W. J. B.: Celiac Disease Associated with Night Blindness and Xerosis Conjunctivae, Tr. Ophth. Soc. U. Kingdom **53**:295, 1933.

81. Wilbur, D. L., and Eusterman, G. B.: Nutritional Night Blindness: Report of a Case, J. A. M. A. **102**:364 (Feb. 3) 1934.

82. Gamble, R. C.: Keratomalacia and Cystic Fibrosis of the Pancreas, Am. J. Ophth. **23**:539, 1930.

83. Jeghers, H.: Night Blindness as a Criterion of Vitamin A Deficiency: Review of Literature with Preliminary Observations of Degree and Prevalence of Vitamin A Deficiency Among Adults in Both Health and Disease, Ann. Int. Med. **10**:1304 (March) 1936-37.

84. Appelmans: Xerosis and Hemeralopia in the Adult, Bull. Soc. belge d'opht. **74**:109, 1937.

85. Wolff, H.: Ulcer of Cornea and A Avitaminosis, Acta ophth. **16**:323, 1938.

86. Patek, A. J., Jr., and Haig, H.: The Occurrence of Abnormal Dark Adaptation and Its Relation to Vitamin A Metabolism in Patients with Cirrhosis of the Liver, J. Clin. Investigation **18**:609, 1939.

87. Wohl, M. G., and Feldman, J. B.: Vitamin A Deficiency in Diseases of the Liver: Its Detection by Dark Adaptation Methods, J. Lab. & Clin. Med. **25**:485, 1940.

eases, fever, hyperthyroidism and pregnancy, to mention only a few, will increase the need for vitamin A, as well as the other elements of the diet. That such is the case has been shown by the observations of Jeghers,[83] Kentgens [88] and Juhasz-Schaeffer.[89]

Therapeutic Methods.—Parenteral Administration: When gastrointestinal disturbances interfere with the proper absorption of vitamin A, parenteral administration of either vitamin A or carotene must be considered. Tai,[14] however, pointed out the contraindication to the use of carotene in hepatic disease; that this is true will be evident if one remembers that the human body cannot utilize carotene as such but must convert it into vitamin A in the liver.

Topical Application: The topical application of carotene (provitamin A) in ocular diseases was first reported on by Balachovski [90] and Ratschewskij [91] in 1934. Two years later Stevenson [92] recommended the local use of cod liver oil for external diseases of the eye. It was only reasonable that numerous animal experiments with reference to the topical use of vitamin A should be carried on. Such a local use of vitamin A in experimentally induced lesions has been favorably reported on by Rinaldi,[93] Heinsius,[94] Frederici,[95] Vanysek [96] and Kapuscinski,[97] but de Rötth,[98] after several series of animal experiments, concluded that there was no difference in the time necessary for epithelization of the denuded cornea in animals without vitamin A deficiency which were treated with cod liver oil and those treated with liquid

88. Kentgens, S. K.: The Relation Between Pregnancy, Disturbance in Dark Adaptation and Vitamin A Content of Blood, Acta ophth. **16**:332, 1938.

89. Juhasz-Schaeffer, A.: Hemeralopia in Pregnancy and Vitamin A, Klin. Wchnschr. **17**:407, 1938.

90. Balachovski, F. A.: Provitamin A as Anti-Inflammatory Factor in Diseases of the Eye, Sovet. vestnik oftal. **4**:470, 1934.

91. Ratschewskij, R. A.: Physiologic and Therapeutic Action of Colloidal Solutions of Provitamin A in Their Local Application to the Eye, Klin. Wschnschr. **13**:918, 1934.

92. Stevenson, E.: Cod Liver Oil as Local Treatment for External Affections of the Eye, Brit. J. Ophth. **20**:416, 1936.

93. Rinaldi, S.: Local Use of Vitamins A and D in Treatment of Corneal Lesions, Ann. di ottal. e clin. ocul. **64**:505, 1936.

94. Heinsius, E.: Experimental Observations as to the Influence of Vitamin A on Regeneration of Corneal Epithelium, Arch. f. Ophth. **136**:103, 1936.

95. Federici, E.: A and D Vitamins in Corneal Reparative Processes, Boll. d'ocul. **16**:357, 1937.

96. Vanysek, J.: The Importance of Vitamin A in Regeneration of Corneal Tissue, Českoslov. oftal. **3**:189, 1937.

97. Kapuscinski, W. J., Jr.: The Action on the Eyes of Rats of a Locally Administered A and the Effect upon This Action of Vitamin D, Arch. f. Ophth. **138**:667, 1938.

98. de Rötth, A.: Local Action of Oils Containing Vitamin A, Arch. Ophth. **24**:281 (Aug.) 1940.

petrolatum. In contradiction to the works of Balachovski and Ratschewskij, Vanysek,[96] experimenting with rabbits, came to the conclusion that carotene instilled directly into the conjunctival sac produced no beneficial effects on artificially induced corneal lesions. In spite of these conflicting reports, Heinsius,[99] de Grósz,[100] Tikhova [101] and many others enthusiastically prescribed local applications of vitamin A in the treatment of such varying conditions as phlyctenular keratoconjunctivitis, trachomatous xerophthalmia, postoperative keratitis, corneal erosion, keratitis neuroparalytica and keratitis bullosa. In ophthalmology, as in the other branches of medicine, an understanding of the etiology of disease processes will result in more logical therapy.

CONCLUSIONS

1. Hypovitaminosis A may exist in persons who presumably are receiving an adequate diet.

2. Even in the absence of demonstrable ocular lesions, poor dark adaptation is not presumptive evidence of vitamin A deficiency.

3. Fasting vitamin A levels of the blood are of value as a diagnostic aid in establishing the existence of a deficiency.

4. More reports on early ocular changes in vitamin A deficiency need to be made before biomicroscopic examination can be a real diagnostic aid.

5. The corneal and conjunctival lesions in vitamin A deficiency are probably neurotrophic, resulting from degenerative changes in the trigeminal nerve.

6. Keratoconjunctivitis sicca is probably one of the many ways in which vitamin A deficiency manifests itself.

7. Some of the heretofore unexplainable ocular congenital anomalies are undoubtedly due to a vitamin A deficiency in the mother at some critical time during the period of gestation.

8. Vitamin A deficiency may be caused by (*a*) reduced consumption; (*b*) defective absorption; (*c*) uneconomical utilization and (*d*) excessive utilization (1) during rapid growth, (2) during illnesses or (3) during pregnancy.

9. Parenteral administration of vitamin A is sometimes indicated.

10. Topical application of vitamin A is of doubtful value.

441 Lowry Medical Arts Building (2).

99. Heinsius, E.: Use of Ointment Containing Vitamin A in Ophthalmology, München. med. Wchnschr. **84**:936, 1937.

100. de Grósz, S.: Local Use of Vitamin A Preparation in Ophthalmic Practice, Arch. Ophth. **22**:727 (Nov.) 1939.

101. Tikhova, V. A.: Local Application of Vitamins in Diseases of Eye, Vestnik oftal. **14**:16, 1939.

News and Notes

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

Home Study Courses, American Academy of Ophthalmology and Otolaryngology.—The Home Study Courses in the basic sciences of the two specialties, sponsored by the American Academy of Ophthalmology and Otolaryngology, will be given again beginning Sept. 1, 1947. Registrations must be completed before August 15. Detailed information may be secured from Dr. William L. Benedict, executive secretary, 100 First Avenue Building, Rochester, Minn.

William Hamlin Wilder Memorial Lecture.—Dr. John Q. Griffith Jr., of the Laboratory for the Study of Hypertension, Philadelphia, will deliver the third William Hamlin Wilder Memorial Lecture of The Institute of Medicine of Chicago on Friday evening, May 23, at the Palmer House, his subject being "Rutin: A Therapy for the Hemorrhagic Complications of Hypertension."

Ophthalmological Study Council.—The Ophthalmological Study Council will give its third, and last, basic course in ophthalmology at Westbrook Junior College, Portland, Me., June 20 to Sept. 13, 1947.

Further information may be secured by writing to the Ophthalmological Study Council, 520 Commonwealth Avenue, Boston.

Stanford University Eye Bank.—Officials of Stanford University have announced the establishment of an eye bank, to be located at Stanford University Hospitals, San Francisco. The eye bank, which is under the direction of Dr. Dohrmann K. Pischel, will be similar to those now established in New York, Boston and Chicago. A bill now pending will, on passage, make it lawful to will eyes in the state of California.

PERSONAL NEWS

Appointment of Executive Director of the National Society for the Prevention of Blindness.—Dr. Franklin M. Foote has been appointed executive director of the National Society for the Prevention of Blindness, succeeding Mrs. Eleanor Brown Merrill, who is retiring.

Dr. Foote was formerly district health officer of the Kips Bay-Yorkville Health District of the Department of Health of New York City. He is assistant professor of public health and preventive medicine at Cornell University Medical College.

A native of Great Barrington, Mass., Dr. Foote holds the B.S., M.D. and D.P.H. degrees from Yale University. During World War II, he served as a major in the Medical Corps of the Army of the United States. He is a member of the American Medical Association, a fellow of the American Public Health Association, a member of the Harvey Society of New York City and a member of the New York County Medical Society and the Medical Society of the State of New York.

SOCIETY NEWS

Pan-American Association of Ophthalmology.—Officials of the Pan-American Congress of Ophthalmology met in New York in February to discuss matters relating to the Third Congress of the Pan-American Association of Ophthalmology.

The date for the Congress has been advanced to Jan. 4 to 10, 1948.

Regulations of the Congress were adopted by the local committee: Dr. Tomas R. Yanes, president; Dr. Gilberto Cepero, general director, and Dr. Miguel A. Branly, general secretary.

The deadline for receipt of papers and lectures and their accompanying summaries is Aug. 27, 1947. (The summaries are limited to 400 or 500 words.) Two complete copies must be sent: one to Dr. Branly, Edificio de la Escuela de Medicina, Calle 25 and I, Vedado, Habana, Cuba, the other, to Dr. Conrad Berens, 301 East Fourteenth Street, New York 3, if the author lives north of Panama, or to Dr. Moacyr E. Alvaro, 1151 Rua Consolacão, São Paulo, Brazil, if the author lives south of Panama. The deadline for receipt of the opening discussions on official subjects is August 23, and these must be accompanied with a résumé of 200 to 300 words. This date also is the deadline for titles of movies for the cinematographic exposition.

Authors wishing to exhibit books, periodicals, etc., must have them in the hands of the local committee by November 30.

One entire day will be devoted to a discussion of the prevention of blindness. Dr. Thomas D. Allen, 122 South Michigan Avenue, Chicago 3, was commissioned to direct the instruction courses in English, to be given January 6, 7 and 8, mornings only.

Dr. Brittain Payne, 301 East Fourteenth Street, New York 3, was commissioned to assemble and direct the scientific exhibit from the English-speaking countries.

Drs. Payne, Branly and Manoel A. de Silva, of São Paulo, were designated assistant secretaries.

The program of all the activities of the Congress will close Aug. 30, 1947.

A copy of the regulations, as well as detailed information on courses, travel, etc., will be sent to all ophthalmologists who by that date have paid their subscriptions.

Subscriptions for the Congress are still open. Those interested may send a postal order or bank draft for $10 to Dr. Branly, to cover the quota for the Congress. If the subscriber is not able to come to Habana, a copy of the transactions, including papers and discussions, will be sent to him when they are published. Hotel reservations will be made through Dr. Branly at the time of receipt of the fee. While subscription fees need not be sent in immediately, hotel reservations cannot be made until they are received; the sooner they are received the easier it will be for the local committee to assign comfortable lodgings.

The local committee wishes to send programs, tickets for courses, registration card, name of hotel and number of room, etc., direct to each member as soon as possible.

The reservations for travel, transport, etc., may be made through any agency. However, arrangements are being made with Mr. Harold

E. Wright, Atlantic Coast Line Railroad, 217 S. E. First Street, Miami, Fla., which organization will arrange transportation especially for the Congress and will conduct postconvention excursions at moderate cost.

Concerning the commercial exhibition, address Dr. Hector Uribe Troncoso, 301 East Fourteenth Street, New York 3; concerning the cinematographic exhibition, Dr. Gilberto Cepero, Calle L no. 353, Vedado, Habana, and concerning the ophthalmologic literature, Dr. Miguel A. Branly. Additional information may be obtained by addressing Dr. Branly.

Reading Eye, Ear, Nose and Throat Society, Reading, Pa.—The joint meeting of the Reading (Pa.) Eye, Ear, Nose and Throat Society and the Diplomates Association of the physicians of Berks County was held Wednesday, Feb. 19, 1947. The meeting was addressed by Dr. Eugene P. Pendergrass, on "Atomic Energy in Medicine."

Correspondence

USE OF EYE BANK EYES FOR TRAINING IN OPHTHALMIC SURGERY

To the Editor:—In an article entitled "The Use of Cadaver and Animal Eyes for Training and Experience in Ophthalmic Surgery" (*Am. J. Ophth.* 21:904, 1938), I pointed out that the eyes of recently deceased persons would be most desirable for the purpose. Unfortunately, not until now has there been any possibility of obtaining such material in sufficient quantity. The Eye Bank for Sight Restoration, Inc., may accomplish this. It has the cooperation of ophthalmic surgeons in sending to the bank eyes enucleated from living persons for various pathologic conditions; and, better still, it has prevailed on members of the profession in general, the hospitals and pathologic laboratories and the public to furnish it with the eyes of recently deceased persons. These eyes may be put to good use not only for transplantation of cornea and for research but, in limited numbers at present, for training and experience in ophthalmic surgery.

There are conditions of the human eye that will yield only to surgical measures, and are not amenable to medical or other therapy. The operative procedure must be skilfully and well carried out, with the confidence born of experience. All ophthalmic surgeons must begin and be trained or acquire skill through self instruction. It is, then, with expressions of great appreciation that they should welcome the work of the Eye Bank for Sight Restoration, Inc.

There is great sentiment, and justly so, connected with the giving of eyes for corneal transplantation to restore the sight of a blind person. There will be just as great sentiment connected with the giving of eyes for the great, and broader, purpose of saving other eyes by skilful surgery. The legal restrictions and other impediments to this end have been removed. A supplementary clause may be added to the permit for autopsy which will authorize the removal of the eyes for the purposes of the Eye Bank for Sight Restoration, Inc. In case autopsy is not permitted or necessary, the eyes may be given anyway, proper permission being arranged.

I wish to express my personal appreciation of the fine manner in which the material lends itself to demonstration of the operation of intracapsular cataract extraction. Teachers and students have all been disappointed in material heretofore available for the purpose but have made the best of it. Cadaver eyes are too necrotic for any such use, while animal eyes have lenses which are too bulky and zonules which are too resistant and resilient to be of any practical use. Even normal monkey eyes are not adaptable, for the latter reason. Eye Bank eyes, however, are perfect for the purpose. The absence of blood permits the surgeon to proceed with the operation in the cool, scientific manner with which he should work on the living eye. Knowledge of the behavior of human tissues gained in such work will engender a confidence which will help much in carrying through a real operation to a successful conclusion.

The eyes to be suitable must be fresh, and must be available not more than one day after death. The eyes should be from adults, so that the size and shape will be that of the average eye on which the surgeon will operate. Decomposition of tissues, particularly of the uveal tissues, proceeds rapidly after death. It may seem to be wishful thinking that the procedures of obtaining the necessary consent, enucleation of the eyes, refrigeration, delivery to the Eye Bank and, then, distribution and use can be accomplished within twenty-four hours, but I believe that with proper organization and planning this can be done.

A further possible use in the future for Eye Bank eyes is that of serving for examination by the American Board of Ophthalmology for the certification of *safe* ophthalmic surgeons and later, after more extended examination, of *expert* ophthalmic surgeons.

It is for these purposes that I laud the work of the Eye Bank for Sight Restoration, Inc., and trust that it will continue its work as it has been begun, that other organizations will not spring up to duplicate the work and cloud the issue or hamper its development, that colleges and other institutions for training in ophthalmic surgery will join with it and, finally, that members of the profession and the public in general will continue in cooperation and appreciation of the work.

DANIEL B. KIRBY, M.D., New York.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Bacteriology and Serology

CLINICAL BACTERIOLOGY AND CYTOLOGY OF SOME OCULAR INFECTIONS. C. WEISS and M. C. SHEVKY, Am. J. Clin. Path. **14:** 567 (Nov.) 1944.

A white man aged 56 had been in an automobile accident in 1941. In July 1943 the right eye was removed because of a "growth." Three months later the patient complained of poor vision in the left eye. Fine deposits were observed on the posterior surface of the cornea and on the anterior surface of the lens. Opacities were present in the aqueous and vitreous. A diagnosis was made of "possible cyst of the retina with retinal detachment and uveitis." The sclera was trephined, and material obtained for culture showed the presence of a yeastlike organism, which was identified as Torula histolytica (Cryptococcus hominis).

W. ZENTMAYER.

Color Sense

IS IT POSSIBLE TO INFLUENCE CONGENITAL COLOR BLINDNESS? E. WOLFFLIN, Ophthalmologica **109:**324 (June) 1945.

The author reviews the work of Studnitz (no references to which are given) on the chemical composition of the material believed to be responsible for the perception of colors. He claims that there are three separate chemical substances, which have different absorption maxima in the various portions of the spectrum, namely in the red, yellow and blue regions. These substances are therefore known as the red, yellow and blue substances. They are found in slight concentration in retinas containing chiefly cones and have been isolated from the oil droplets in the cones of certain animals. Their chemical nature seems to be that of carotenoids. The red substance is recognized as astaxanthin; the yellow substance, as xanthophyll, and the blue substance, as lacertofulvin. At present, these substances cannot be produced in sufficient quantities to test their effectiveness when supplied to the color blind by oral administration, but the author believes that it may be possible to influence color vision by such treatment. No data of any experimental work are given.

F. H. ADLER.

Conjunctiva

CONJUNCTIVAL HEMORRHAGE DUE TO AN INFECTION OF NEWCASTLE VIRUS OF FOWLS IN MAN (LABORATORY AND CONTACT INFECTION). N. I. SHIMKIN, Brit. J. Ophth. **30:**260 (May) 1946.

A laboratory assistant, while giving poultry injections for protective vaccination of amniotic fluid from a chicken egg (dilution 1:3,000),

touched the upper lid of the left eye with the forefinger. This was followed by soreness and redness. Later, along the entire length of the eyelid was a subcutaneous hemorrhage, and a heavy subconjunctival hemorrhage covered the upper and outer part of the bulbar conjunctiva. The symptoms disappeared without complications.

W. ZENTMAYER.

SURGERY OF PTERYGIUM. ALTINO VENTURA, Rev. brasil. de oftal. **4:** 188 (Dec.) 1945.

Paulo Filho's technic of conjunctival autoplasty is described. The author states that he has performed 52 operations of this type and has observed only 3 recurrences. He had always used McReynolds technic but has found that the percentage of recurrences was slightly higher with this method than with that of Paulo Filho.

M. E. ALVARO.

TREATMENT OF GONOCOCCIC CONJUNCTIVITIS AND SERPIGINOUS ULCER OF THE CORNEA WITH SULFONAMIDE COMPOUNDS. E. WEISZLOVITS, Ophthalmologica **108:** 121 (Sept.) 1944.

Local application of sulfacetimide produced rapid disappearance of the inflammation and the gonococci. In a number of cases of ophthalmoplegia neonatorum the condition cleared up in four to five days; in others, in ten days. The combined local and internal administration of sulfacetimide produced a considerable shocking in the period of treatment. The authors also found that cases of serpent ulcer were favorably treated by combination of the administration of sulfacetimide and "shock therapy" with sulfathiazole.

F. H. ADLER.

Experimental Pathology

RELATION OF THE EYE TO IMMUNITY IN SYPHILIS, WITH SPECIAL REFERENCE TO THE PATHOGENESIS OF INTERSTITIAL KERATITIS. A. C. WOODS and A. M. CHESNEY, Am. J. Ophth. **29:** 389 (April) 1946.

A series of experiments indicate that (1) the corneas of rabbits with experimental syphilis do not always share in the immunity to reinfection which develops during the course of the syphilitic infection; (2) direct inoculation of the cornea is followed by the development, in that tissue, of a local resistant state toward the organisms, although in some instances the protection thus conferred is either not absolute or not permanent; (3) vascularization of the cornea appears to be a factor in influencing favorably the development of a local resistant state. It is suggested that the usual late occurrence of interstitial keratitis may be due to a combination of lack of local immunity in the cornea and the occurrence of minor traumatic incidents as the initiating factor. It is also suggested that the healing of the lesions of interstitial keratitis when vascularization occurs is due to the development of a local immunity, presumably through antibodies coming from the blood.

W. S. REESE.

Injuries

PENETRATING WAR WOUNDS OF THE EYE AND ORBIT. H. H. SKEOCH, Brit. J. Ophth. **29**:113 (March) 1945.

Military ophthalmic surgery is at present chiefly concerned with penetrating wounds due to high velocity fragment missiles resulting from high explosive action, the cause of 99 per cent of battle casualties and accidents necessitating operation by the military ophthalmic surgeon. The other 1 per cent of wounds are due to flying steel chips resulting from striking cold steel with a steel hammer, the commonest cause of intraocular foreign bodies in civilian life.

Wounds of the eye and orbit due to high explosive action are often multiple, with additional wounds of the head, face, nose and ears, a situation which suggests cooperation in operative procedures on these parts.

After a long trial, the equatorial ring method of roentgenographic localization has proved its worth and is recommended as a routine. The method of removal of foreign bodies by the posterior route is to be recommended because it permits the use of the small electromagnet and provides the nearest and most effective approach of the point of the magnet to the foreign body, and therefore the shortest and most direct line for its removal.

The article is illustrated.

W. ZENTMAYER.

INTRAOCULAR FOREIGN BODY AND SIDEROSIS BULBI. W. CARVALHO PINTO and J. MENDONCA DE BARROS, Arq. brasil. de oftal. **8**:71 (June) 1945.

The authors present a detailed case history of an intraocular foreign body which had lodged in the eye a year and a half before examination, the patient having come for an examination because lime had dropped into his eye and vision had decreased. After extraction of the foreign body an operation for cataract was performed a month later. Sena's statistics on the site of penetration, localization and nature of foreign bodies are given. A bibliography is furnished.

M. E. ALVARO.

CHANGES IN THE FUNDUS IN CASES OF MILITARY INJURIES OF THE EYE. O. SHERESHEVSKAYA, Vestnik oftal. **23**:31, 1944.

War injuries of the eye are a combination of direct trauma to the tissues and secondary degenerative processes, which appear later and present a varied ophthalmoscopic picture and a difficult diagnostic problem.

Shereshevskaya made examinations in 300 cases for lesions of the fundus after injuries to the orbit and face, general contusions and injuries of the eyeball. Changes in the fundus were found in 76 per cent of all cases of injury of the posterior segment of the eye by fragments and shells. Unilateral changes were found in 68 per cent and bilateral changes in 7 per cent of cases, and in 25 per cent one eye was either enucleated or there were serious injuries of the anterior segment of the eye, followed by blindness.

The choroid was most frequently injured. Ruptures were of varied shapes and sizes, ranging from punctate lesions to ruptures involving

one-half the eyeball, followed at times by massive hemorrhages. The proliferated connective tissue could be mistaken for detached retina, but as a rule with large ruptures of the choroid the exudative inflammation and scarring prevented retinal detachment; only in 2 cases was retinal detachment observed. The secondary changes of choroidal injuries were inflammatory chorioretinitis, ascending atrophy of the optic nerve and degenerative maculitis. Retinal tears were observed less frequently and occurred as holes, mostly in the macular region but at times at the periphery. Retinal detachments were rare.

The macular region was affected frequently as a result of the injury to the choroid and retina and of hemorrhages, and because of the reduction of vision the condition was most serious. In some cases connective tissue formed, and the resulting lesion resembled disciform macular degeneration. Punctate macular hemorrhages were seen often.

Evulsion of the optic nerve was present in 3 cases. In all there were enophthalmos and limitation of motion of the eyeball.

O. SITCHEVSKA.

Methods of Examination

TECHNICAL REFINEMENTS IN THE REMOVAL OF MAGNETIC FOREIGN BODIES FROM THE POSTERIOR SEGMENT OF THE EYE. G. C. STRUBLE and L. J. CROLL, Am. J. Ophth. **29:**151 (Feb.) 1946.

Struble and Croll stress the pinpoint localization of foreign bodies, a painstaking layer dissection of the sclera between scleral retraction sutures and removal of foreign bodies from the posterior segment without penetrating the choroid or pars plana with the magnet tip. The localization is done by means of a small lead plate sewn to the sclera.

W. S. REESE.

LOCALIZATION OF INTRAOCULAR FOREIGN BODIES. E. W. PERKINS, Bull. U. S. Army M. Dept. **5:** 215 (Feb.) 1946.

No one method of localization of intraocular foreign bodies solves all the problems encountered in battle. Perkins has found the silver wire ring which fits around the equator of the globe to be the simplest method of determining whether or not a deeply embedded foreign body is just within or just outside the eye. It does not give the exact localization so well as the more elaborate methods, but this does not lessen its practical value. The equipment, technic and interpretation of the films are described, and 1 illustrative case report is given. The article is illustrated.

W. ZENTMAYER.

UTILIZATION OF THE CAMPIMETER WITH REDUCED ILLUMINATION FOR THE MEASUREMENT OF RETINAL ADAPTATION. R. WEEKERS and F. ROUSSEL, Ophthalmologica **110:**242 (Nov.-Dec.) 1945.

The state of retinal adaptation alters the position of the isopters considerably when these are measured under conditions of reduced illumination (less than 30 lux). If the rods function normally, one should find a progressive increase in the field of vision under these condi-

tions. If the rods are not functioning normally, the field of vision will contract. This test constitutes a reliable and sensitive quantitative means of detecting night blindness. Quantitative deficiencies, chiefly of proteins and lipids, cause a concentric contraction of the field when the illumination is reduced. In order to bring out a scotoma of slight intensity, the field of vision should be measured with reduced illumination, but it is important if one is using this method to appreciate that the state of retinal adaptation tends to alter the position of the isopters and that night blindness can cause a definite contraction of the field under these conditions.

F. H. ADLER.

Orbit, Eyeball and Accessory Sinuses

OCHRONOSIS-LIKE PIGMENTATION ASSOCIATED WITH USE OF ATABRINE [QUINACRINE]. H. S. SUGAR and W. W. WADDELL, Illinois M. J. **89:** 234 (May) 1946.

Sugar and Waddell observed in 10 men who had been treated with quinacrine for considerable periods an ochronosis-like pigmentation never described before. These pigmentary deposits are most characteristically seen as a gray-blue discoloration in the bony palate, where it ends as a sharp line at the transition to the soft palate. A gray-blue pigmentation of some or all of the nail beds is the next most obvious sign. This is manifested either as a transverse band at or near the middle of the nail or as a diffuse discoloration of the entire nail bed. The next most obvious finding was pigmentation of the conjunctiva in the area of the palpebral fissure. The conjunctival pigment extended in patches of varying size from the nasal and temporal sides of the cornea and involved the corneal limbus nasally and temporally, less frequently below, and in 2 cases involved the plica semilunaris and the caruncle. The pigment appeared to lie at varying depths. Biopsy in 1 case showed that the pigment lies both in the basal layer of the epithelium and below it. This pigmentation associated with the use of quinacrine requires no treatment and is important only in differential diagnosis. The pigmentation may cause considerable concern to some patients. Among the conditions with which it may be confused are carotenemia, Addison's disease, icteric disease, picric acid poisoning, ochronosis due to phenol poisoning and alkaptonuric ochronosis.

J. A. M. A. (W. ZENTMAYER).

THE FIRST EXPERIMENT IN PROSTHESES OF THE ORBIT MADE OF PLASTIC MATERIAL. D. SUDAKEWITCH, Vestnik oftal. **6:** 43, 1944.

The process of preparing the plastic material for prostheses for the orbit, which was done in dental laboratories, is described in detail. These prostheses are light, transparent and of a pleasing color, so that they look natural. The prosthesis is held by a wire frame and is attached to the bridge of the frame, and it does not interfere with the movement of the face. Three cases of severe injuries of the orbit, involving the zygomatic, the nasal and the maxillary bones, are reported. In all these cases the cosmetic result was good. Sudakewitch believes

the ophthalmologist should know the technic of the prosthesis, so that he can give certain recommendations to the technician.

O. SITCHEVSKA.

Operations

HETEROGENOUS CONJUNCTIVAL TRANSPLANTATION. E. ROSEN, Am. J. Ophth. **29:** 193 (Feb.) 1946.

Rosen refers briefly to Filatov's work on grafting animal conjunctiva and summarizes his work. He reports a case in which he used cadaver conjunctiva successfully as a graft in a case in which there was an adhesion between the upper lid and the globe, producing ptosis. He suggests that cadaver conjunctiva in refrigerated or unrefrigerated form may be used in a great many conditions. W. S. REESE.

PLASTIC EYE IMPLANT. A. D. RUEDEMANN, Am. J. Ophth. **29:** 947 (Aug.) 1946.

Ruedemann describes an operation in which he implants a plastic globe in the orbit after enucleation. To this he attaches the rectus muscles. Although the procedure is time consuming and difficult, he states that the efforts are justified by the results. W. S. REESE.

OPHTHALMOPEDICS. J. J. KOHOUT and A. CALLAHAN, Am. J. Ophth. **29:** 968 (Aug.) 1946.

Kohout and Callahan describe the use of ophthalmopedics in cases of enucleation and evisceration, contracted socket, wrinkling of the skin complicating lid reconstruction, edema of the lids and ptosis; as an aid in seating abnormally prominent artificial eyes, and in complete loss of eyelids and the orbit. Each ophthalmopedic is first made up in a combination of paraffin and base plate wax. W. S. REESE.

Physiology

THE RELATIONSHIP BETWEEN LIGHT ADAPTATION AND DARK ADAPTATION AND ITS SIGNIFICANCE FOR APPRAISAL OF THE GLARE EFFECT OF DIFFERENT ILLUMINANTS. E. SIMONSON, S. S. BLANKSTEIN and E. J. CAREY, Am. J. Ophth. **29:** 328 (March) 1946.

The authors found no consistent relationship between speed of light adaptation and that of dark adaptation. For the speed of light adaptation the duration of exposure appears to be of greater importance than the brightness at low levels of brightness, whereas with higher illumination the brightness is more important. Daily variations of light and dark adaptation do not coincide. W. S. REESE.

A CENTER FOR OCULAR DIVERGENCE: DOES IT EXIST? R. G. SCOBEE and E. L. GREEN, Am. J. Ophth. **29:** 422 (April) 1946.

Scobee and Green review the theory of passive divergence due to elasticity of the orbital structure and put forward further clinical evi-

dence to substantiate it. It would thus seem that the majority of phenomena can be adequately explained on the basis of a single vergence center in the brain (a convergence center).

W. ZENTMAYER.

Retina and Optic Nerve

A CASE OF ECLIPSE BLINDNESS. N. A. JEVONS, Brit. J. Ophth. **30:** 84 (Feb.) 1946.

A man aged 25, on the day following the observation of a partial eclipse of the sun both with and without a protecting screen, mostly with the right eye, found his vision blurred. The only abnormal ophthalmoscopic finding was a circular hole of about ⅛ disk diameter, with a flat base and steeply sloping sides and surrounded by a zone of edema; visual acuity was 6/18 part. There were an absolute central scotoma of 1 degree and a relative scotoma of 2.5 degrees. There was also a positive scotoma. One month later the only change was the appearance of small, irregular patches of fine pigmentation around the hole.

The article is illustrated.

W. ZENTMAYER.

A CURIOUS LESION OF THE FUNDUS. P. PANNETON, Arch. d'opht. **5:** 328, 1945.

The author describes the case of a patient aged 44 who came for examination, during the course of which ophthalmoscopic examination of the left eye revealed a whitish mass about one-third the size of the disk in the upper temporal border of the fundus, surrounding the blood vessels. Vision in this eye was 0.9. In an attempt to explain this lesion, the author considers the possibility of tuberculosis, of hyaline deposits, of Coats's disease, of a malignant growth and of congenital anomalies. The patient was otherwise in good health.

L. B. MARLOW.

OGUCHI'S DISEASE, TYPE 1, IN THE NETHERLANDS: REPORT OF THE FIRST CASE. J. TEN DOESSCHATE, Ophthalmologica **108:** 1, 1944.

This is a review of the literature on Oguchi's disease (congenital night blindness), together with the report of a case. The author criticizes Nakamura's concept of the pathogenesis of the disease.

F. H. ADLER.

TREATMENT OF THROMBOSIS OF THE RETINAL VEINS WITH DICUMAROL. J. D. BLUM and H. JEANNERAT, Ophthalmologica **108:** 129, (Sept.) 1944.

In 7 cases of thrombosis of a retinal vein—of the central vein in 3 and of branches of the vein in 4—treatment consisted in a combination of dicumarol and heparin. In 2 of the cases roentgen therapy was also given. The authors feel that the results were encouraging and that theoretically this method should offer the best treatment of this condition. In order to avoid complications, they suggest that the patient's prothrombin level be repeatedly determined.

F. H. ADLER.

TISSUE THERAPY OF RETINITIS PIGMENTOSA. A. LIPKINA, Oftal. J. 2: 29, 1946.

Tissue therapy was applied in 30 cases of advanced, long-standing retinitis pigmentosa. The therapy consisted either of injections of aqueous extract of leaves of aloe conserved in the dark, or of injections of this substance combined with implantation of conserved cadaver skin. The time of observation was from six to twelve months. In cases in which five to eight injections of extract of aloe gave no results, implantation of skin was also made. The conclusions are as follows:

1. Injections of aqueous extract of conserved, autoclaved leaves of aloe constitute an effective therapeutic measure in the control of such a severe progressive degenerative process in the retina as retinitis pigmentosa.

2. It is possible through the aid of tissue therapy to obtain improvement of vision, enlargement of the visual fields and usefulness of the worker.

3. The most effective method of treatment was injection of 0.5 cc. every other day.

4. The combination of injections of leaves of aloe with implantations of skin was the most effective.

A detailed description of preparation of the leaves of aloe and of the skin is given. Tables illustrate the improvement in vision, visual fields and dark adaptation.

OLGA SITCHEVSKA.

Tumors

THE REMOVAL OF ADJACENT NEVI OF THE EYELIDS. A. CALLAHAN, Am. J. Ophth. 29: 563 (May) 1946.

Callahan removed adjacent nevi on the right upper outer margin of lid with a diathermy cutting current and covered both defects with a free graft from the opposite upper lid. Subsequently, an incision was made through the center of the grafted tissue, and another graft from the brow was used to furnish lashes.

W. S. REESE.

CAVERNOUS HEMANGIOMA OF THE ORBIT SUCCESSFULLY REMOVED BY SHUGRUE'S OPERATION. M. PAUL, Brit. J. Ophth. 30: 35 (Jan.) 1946.

A Singalese man aged 52 for six months had had progressive proptosis of the left eyeball. At the time of examination the eyeball was almost protruded from the orbit.

Incipient cataract was present. The fundus was normal. A roentgenogram showed no involvement of the cranial bones by the growth. The approach to the tumor was by the Shugrue technic. The tumor was "the size of a marble" and was encapsulated. Microscopic examination showed that the mass was composed of cavernous blood-containing spaces, lined with a well developed layer of endothelium.

The experience with the Shugrue operation in this case suggests that excision of the outer wall of the orbit does not in itself appreciably interfere with the function of the eye nor is the deformity particularly noticeable. The article is illustrated.

W. ZENTMAYER.

Therapeutics

PENICILLIN TREATMENT OF OCULAR INFLAMMATION. I. C. FRASER and A. A. B. SCOTT, Brit. J. Ophth. **30:** 168 (March) 1946.

Of 20 patients with blepharitis treated with penicillin 9 showed apparent clinical cure, and of the others all but 2 were greatly improved; of 4 patients with acute conjunctivitis all were cured; of 6 patients with keratitis or corneal ulceration 4 were cured. Two patients with Eales' disease were not benefited, but it may be worth investigating the use of penicillin in those cases of acute perivasculitis of the retina in which it is thought that a mild septicemia is the cause.

W. ZENTMAYER.

PENICILLIN IN OPHTHALMOLOGY. Leading Article, Brit. M. J. **1:** 17 (Jan. 5) 1946.

While the purulent infections of the outer eye responded readily to general sulfonamide therapy, the intraocular inflammations as a rule responded but poorly. This was particularly interesting, as the sulfonamide compounds easily penetrated into the interior of the eye. The writer states that there is no real clinical support for the observation that the sulfonamide drugs are effective in treatment of infections of the outer eye when used locally and that there is little justification for the widespread and misguided local use of these remedies. Sulfonamide therapy of ocular diseases is thus largely by oral administration of the drug.

Experience with penicillin runs counter to that obtained with the sulfonamide compounds. In contrast, penicillin does not readily penetrate into the interior of the eye when administered intramuscularly. This is a subject which requires further study. For the present it must be accepted that the use of penicillin intramuscularly, in contrast to general sulfonamide therapy, has but little scope in infections of the inner eye. In striking contrast is the local action of penicillin. Since penicillin is not inactivated by pus or peptone, it has proved invaluable in local medication. The limit of local tolerance has been found to be about 2,500 units per cubic centimeter when used in the form of drops. Ointments have not been employed widely, as no adequate base has been available and most of the ointments have been quickly inactivated and have become irritants. Since penicillin fails to pass the blood-aqueous barrier, injection directly into the aqueous and vitreous has been tried, and it has been found that small quantities can be injected without damage. The limit of tolerance of the anterior chamber is about 200 units, and that of the vitreous is perhaps less. It has been found experimentally that the injection of massive quantities of penicillin into the vitreous produces extensive damage. The great difficulty is the maintenance of the concentration. A solution containing 2,500 units per cubic centimeter instilled in the form of drops at intervals of five minutes caused a rapid clearing of the infection in cases of ophthalmia neonatorum.

In conclusion, the article discusses the possibility that penicillin will prove of value in the treatment of trachoma and of ocular syphilis. Little is to be hoped for from the general administration of penicillin in

treatment of ocular diseases, and for the present the scope of the drug is confined to its local use in external infections of the eye.

Opinions in the United States are at variance with the writer's on the efficacy of the local applications of the sulfonamide drugs and of the introduction of penicillin into the eye.

ARNOLD KNAPP.

USE OF PRIVINE IN OPHTHALMOLOGY. H. ARRUGA, Barcelona, Spain, The Author, 1946.

The author refers to the articles on Privine hydrochloride which have emanated from the eye clinics in Geneva and Basel and reports on his own observations. Privine is a vasoconstrictor of longer duration but of less effectiveness than epinephrine which is well tolerated and does not cause paralytic vasodilatation. It is useful in chronic conjunctivitis, conjunctival hyperemia and allergic and vernal conjunctivitis. It is made up in a solution of 1 : 1,000 and is instilled twice daily, morning and evening.

ARNOLD KNAPP.

PENICILLIN TREATMENT OF LATE INFECTION FOLLOWING FISTULATING OPERATION. G. RONNE, Ophthalmologica **111**:1 (Jan.) 1946.

Four cases are reported of late infection following trephination for chronic simple glaucoma in which penicillin proved of value. The author advises a subconjunctival injection of penicillin supplemented with instillations. The dose should be at least 5,000 Oxford units. He believes that the higher the concentration of penicillin and the shorter the intervals between the administrations, the shorter will be the total time of treatment. In all these cases cultures and smears may show staphylococci. In 1 case of gram-negative micrococcus was also seen. Twenty-four hours after the treatment with penicillin was instituted all the cultures were sterile.

F. H. ADLER.

TISSUE THERAPY IN TRACHOMATOUS PANNUS. D. BUSHMITCH, Oftal. J. **2**:22, 1946.

Tissue therapy was applied in 33 cases of severe, long-standing forms of pannus which did not respond to any other method of treatment. In 30 of these cases there was marked infiltration of the conjunctiva of the lids and fornices.

Tissue therapy was carried out in the following manner: Subcutaneous injections of 1 cc. of extract of leaves of aloe were given every other day, from twenty-five to forty injections being given. After the tenth injection, implantation of conserved cadaver skin was made under the skin of the right and left side, with an interval of about a week between the two implantations. Locally, the patients were getting only a solution of 0.5 per cent zinc sulfate; in cases of ulceration of the cornea atropine sulfate was used.

In the majority of cases the trachomatous process was greatly improved, with decrease in the infiltrations, scarring and clearing of the pannus. The ulcers were covered with epithelium after two or three injections of the extract of aloes. In 22 cases the time of observation

was from four to ten months. In 43 eyes vision was increased from finger counting to 0.1, 0.5 or 0.8. No recurrence was observed.

Thus, Bushmitch considers therapy with biogenic stimulators very effective in cases of advanced trachoma and pannus.

OLGA SITCHEVSKA.

METHODS OF TISSUE THERAPY: TREATMENT WITH BIOGENIC STIMULATORS. V. P. FILATOV, Vestnik oftal. **25:3**, 1946.

Tissue therapy is based on the introduction into the recipient's organism of conserved autogenous and heterogenous tissues and of substances of vegetative origin. It originated in Filatov's observation that when additional corneal elements were transplanted around a corneal transplant the corneal tissue conserved at a low temperature acted more favorably on the clearing of the transplant than the fresh cornea.

Animal tissues conserved at a temperature of from 3 to 4 C. and leaves of plants kept in the dark, owing to the unfavorable conditions under which they are placed, react in a biochemical reconstruction by producing special substances. Filatov named these substances "resistance substances" or "biogenic stimulators." When introduced into the patient's organism, they stimulate his regenerative processes, increase the cellular metabolism and the physiologic function of the cells and most likely reconstruct the fermentative function of the proteins. This explains why tissue therapy is effective in a wide range of diseases, whether of inflammatory or of degenerative origin. Thus, tissue therapy gave excellent results not only in many ocular diseases—interstitial keratitis, opacities in the vitreous, myopic chorioretinitis, pannus and uveitis—but also in general diseases, such as tuberculosis of the pharynx, contracture of joints, psoriasis, neuritis and various arthropathies. This wide field of action of the biogenic stimulators indicates their nonspecificity.

In this article Filatov gives general instructions as to the use of tissue therapy.

Implantation of Tissue.—A detailed description of the preparation of the skin of the cadaver and the technic of the implantation is given. The strip of skin with a thin layer of subcutaneous fat, taken from the cadaver, is cut into pieces and placed in a jar in the refrigerator for six days. On the day of the operation, the skin is sterilized in the autoclave at 120 C. (1½ atmospheres for one hour). The conserved piece of skin, 6 to 8 cm. in size, is implanted into an incised pocket in the patient's skin. The site of implantation may be the abdomen, the thigh or the axillary region. The size of the incision is from 5 to 7 cm. Sutures are applied and removed in a few days. This procedure is simple and painless and may be done on ambulatory patients. A second implantation can be made in two to four weeks. In some cases Filatov combines subcutaneous injections of extracts of conserved tissues with the implantation.

Placenta: Placenta is obtained immediately after birth. A piece is put in the refrigerator for six days; it is then autoclaved, and a piece from 6 to 8 cm. is implanted in the same manner as that employed with skin. Similar implantations can be made of testis, muscle, sclera or cornea and of heterogenous material, such as skin, spleen and muscle of animals, which can be obtained at slaughter houses. A small piece of placenta (2 by 2 by 2 mm.) can also be implanted into a small pocket

made in the conjunctiva of the lower cul-de-sac; no sutures are necessary, as pressure on the lips of the wound with forceps for a few seconds will keep the wound closed.

Injections.—Extract of Placenta: A piece of conserved placenta is cut into minute pieces and mashed into a cereal-like material. To 10 Gm. of the latter 100 cc. of distilled water is added; the mixture is shaken and kept for one hour at room temperature. It is then boiled for one or two minutes in a double boiler. The mixture is filtered through a few layers of gauze, heated again to the boiling point and then filtered again through filter paper. The filtrate is put into ampules of 1 or 2 cc.; the ampules are sealed and sterilized in the autoclave at 120 C. for one hour. The ampules can be kept in the refrigerator for a few months under routine bacteriologic control. Injections of this extract are made subcutaneously daily or every other day, for a total of twenty to thirty injections. They can be repeated in one or two months. If the injections are painful (usually they are not), 0.5 cc. of procaine hydrochloride may be injected previously. Similarly prepared extracts of skin, testis, nerve and other tissues can be used for subcutaneous injections. Since the boiling, filtering and sterilization deprive the extract of proteins, no anaphylactic symptoms have been observed.

Material of Vegetative Origin: Leaves of aloe are put on a plate in the refrigerator at a temperature of 4 to 10 C. for fifteen days (complete darkness). After this period the thorns are removed, and the leaves are washed and cut into small pieces, placed in jars and sterilized in the autoclave for one hour at 120 C. Implantations of pieces of the aloe are made in a manner similar to implantations of skin.

Extracts of leaves of aloe are prepared as follows: The leaves, conserved in the dark for fifteen days, are cut into very small pieces and then mashed into a soft mixture. To 10 Gm. of this mixture is added 50 cc. of distilled water. The solution is kept at room temperature for one hour. It is then boiled for one or two minutes, filtered through gauze twice, then boiled for a few seconds again and finally filtered through paper. The solution is placed in ampules, which are sealed and sterilized in the autoclave. Routine bacteriologic control is observed. The ampules can be kept in the refrigerator for five months. Injections (1 to 4 cc.) are made subcutaneously daily or every other day, until from twenty-five to forty are given. The course of injections can be repeated in a month.

Tissue therapy has been used widely in the Soviet Union. Tissue therapy, Filatov states, "is the general principle of therapeutic medicine," and clinicians can improve on the details as they use it with the various diseases.

OLGA SITCHEVSKA.

DATA ON TISSUE THERAPY IN THE EYE CLINIC OF THE FIRST MOSCOW MEDICAL INSTITUTE. A. CHENTSOV, Vestnik oftal. 25: 30, 1946.

Chentsov tried Filatov's method of tissue therapy in the eye clinic of the First Moscow Medical Institute, chiefly on patients with high myopia and its complications. This report is a preliminary and a cautious one, as only 66 cases were observed. The author states that more observations are necessary and that for a number of diseases this method may prove as useless as have previous methods. Changes

in the macula were seen in 23 cases, hemorrhages in the retina in 5 cases, opacities in the vitreous in 19 cases, detachment of the retina in 3 cases, optic atrophy in 5 cases, uveitis in 4 cases and keratitis in 1 case.

Implantation of conserved cadaver skin was used chiefly. In some cases two or three implantations were made. In 3 cases a piece of placenta was implanted under the conjunctiva, but it produced severe irritation of the conjunctiva and was discarded. In six cases the implant did not take; the wound reopened in four to six days, and the implanted skin was "expelled." In some cases preliminary treatment with injections of cod liver oil was given, but in the majority of cases infiltrates formed at the site of the injection, with elevation of the temperature.

In the series of cases of maculitis, there was improvement of vision of 0.1 or 0.2 in 17 cases and no change in 6. In 3 of the cases of hemorrhage into the macula lutea there was some improvement of vision. The best results were obtained in cases of opacities of the vitreous (19), vision being increased from 0.1 to 0.3 in all cases. Of 3 cases of retinitis pigmentosa, there was no improvement in 2, while in the third case vision increased from 0.1 to 0.2 in one eye and the visual fields were enlarged from 10 to 20 degrees in each eye. In cases of optic atrophy and of uveitis there was no improvement, while in a case of interstitial keratitis vision was greatly improved.

The general condition of the patients was notably improved as a result of the tissue therapy; they felt stronger and "younger," and arthritic pain was relieved.

In conclusion, Chentsov recommends the accumulation of more facts and the treatment of more patients with this method, which he regards as a kind of *Reizterapie*.

OLGA SITCHEVSKA.

Toxic Amblyopia

QUININE AMBLYOPIA. A. BISHAY, Brit. J. Ophth. 30: 281 (May) 1946.

Within a period of two years Bishay saw 7 cases of quinine amblyopia in a district in upper Egypt, which had a severe epidemic of malignant malaria. The case histories are tabulated. Three important conclusions were reached from dealing with these cases: The amount of quinine that the patient takes need not be large, as described by all other authors. Neither the vascular nor the toxic theory explains all cases, and the author believes that there is another element, i. e., sensitiveness of the patient to quinine. In treatment, paracentesis immediately performed produces best and quickest results.

W. ZENTMAYER.

Society Transactions

EDITED BY DR. W. L. BENEDICT

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

Oct. 24, 1946

Burton Chance, M.D., *Chairman*

George F. J. Kelly, M.D., *Clerk*

Adenocarcinoma of the Lacrimal Gland Following a Mixed Tumor of Twenty-Five Years' Duration. DR. I. EDWARD RUBIN (by invitation).

Mixed tumor of the lacrimal gland is rare, less than 300 cases having been reported in the literature. It is the commonest disease of the lacrimal gland. The origin of this tumor is not established. Grossly and histologically it resembles mixed tumor of the salivary gland.

The signs and symptoms of mixed tumor of the lacrimal gland are those of a slowly progressive, unilateral, orbital growth. These include proptosis, with displacement of the globe downward and slightly nasalward. A mass felt in the region of the lacrimal gland is a constant diagnostic sign. There are also limitation of motion, diplopia, impairment of vision, fundic changes, lacrimation and exposure keratitis; there is usually no pain.

Recurrence of this tumor is common. The growth is often incompletely removed, and it has a strong tendency to bony invasion. It may become malignant after many years.

Roentgen therapy has little noticeable effect. Surgical removal is the best therapeutic measure and should be as radical as possible. If bone is invaded, it should be resected. If the orbital tissues are involved, immediate exenteration is indicated.

Four surgical approaches are discussed: the direct, the transconjunctival, the Krönlein and the frontal flap, with removal of the roof of the orbit.

A case of mixed tumor of the lacrimal gland in a white man aged 35 was presented. The case had been followed from childhood. At the age of 10 years proptosis was first noted. At the age of 16 years a mixed tumor of the left lacrimal gland was supposedly completely excised. Eleven years afterward the tumor first recurred, and it was excised five years later, at the age of 33. The microscopic diagnosis was "mixed tumor." Within twenty-one months it recurred, and this time it involved the optic nerve, producing papilledema. Intracranial extension was suspected; so a frontal craniotomy, with removal of the roof of the orbit, was performed. This was followed by complete exenteration of the orbit. A large tumor, apparently arising from the region of the lacrimal gland, extended posteriorly to compress the optic nerve. The pathologic report was adenocarcinoma.

In conclusion, I wish to thank Dr. Spaeth for the privilege of presenting this interesting and unusual case. I also wish to acknowledge Dr. Zentmayer's cooperation in this follow-up report on the case he presented eighteen years ago.

DISCUSSION

DR. JACOB H. VASTINE II: Dr. Rubin has made such a complete presentation of this subject that little remains to be discussed.

Surgical intervention is probably the treatment of choice in cases of mixed tumor, whether of the salivary glands, the nasal accessory sinuses or the lacrimal gland. In some cases operation is impossible or is refused, and in these cases irradiation has value. This may be administered either as roentgen or as radium therapy or as both. The irradiation may be expected to effect regression of malignant tissue and to retard the growth of the benign elements. There is sufficient proof of the value of irradiation to recommend it as a postoperative measure.

It is interesting to note that this patient was first operated on in 1927. He received immediate postoperative roentgen therapy, administered by Dr. Henry Pancoast, and did not have a recurrence for eleven years. He was treated by me in 1939 and 1940, and the tumor remained stationary until 1944. He was again operated on in 1944 and at that time received no postoperative roentgen therapy. It is striking that there was a rapid recurrence and that within two years another tumor was removed from the same site. This time it was malignant. The question may be asked whether postoperative treatment in 1944 would have delayed recurrence or malignant change.

Roentgenograms which I made in 1939, and again in 1946, showed pressure erosion of the roof of the orbit in the region of the lacrimal fossa. This defect remained unchanged.

Roentgenograms and photographs were presented of an unconfirmed case in which treatment was carried out by Dr. Pfahler and me in 1930. There were marked ptosis and proptosis, which regressed after roentgen therapy alone. The patient had been studied by Dr. Goalwine in New York in 1930, at which time a defect in the lacrimal fossa of the orbit was noted. This was similar to the erosion in the case presented by Dr. Rubin. That patient was referred to Dr. Pfahler for roentgen therapy in 1930. A presumptive diagnosis of mixed tumor of the lacrimal gland was made. Roentgen therapy alone was administered by Dr. Pfahler and by me. The patient was entirely well when last seen, five years later.

DR. ROBERT A. GROFF: In Dr. Rubin's case, it was thought prior to operation that the orbital tumor had entered the orbit through the bony defect in the orbital roof seen in the roentgenogram, or that it had extended along the optic nerve into the cranial cavity. When the anterior fossa was explored, there was no evidence of tumor. On removal of the roof of the orbit, it was obvious that the tumor had extended throughout the tissue in the orbit, and it was difficult to identify normal structures. For this reason, I contented myself with excising part of the tumor, with the idea that Dr. Spaeth should later remove the entire contents of the orbit.

The procedure of frontal craniotomy and removal of the roof of the orbit is simple and safe. It is done entirely extradurally, so that the subdural and subarachnoid spaces are not entered or contaminated. This method affords excellent exposure of the structures in the orbit, and I commend it not only as an easier means of removing orbital tumors completely but as the procedure for decompression in cases of exophthalmos. The procedure should be carried out jointly by the neurosurgeon and the ophthalmologist. Even though Dr. Spaeth has given me the opportunity on many occasions to expose the orbit by this procedure, and I have certain knowledge of the structures within the orbit, I much prefer him, or one of his associates, to do or guide the intraorbital portion of the operation.

DR. EDMUND B. SPAETH: As soon as I received the report of the biopsy from Dr. Groff's transfrontal operation, I did a radical exenteration of the orbit. The reason for the massive and immediate postoperative radium therapy was not the original mixed cell tumor but the report of a clearcut, rapidly developing adenocarcinoma.

My associates and I have another case of mixed cell tumor of the lacrimal gland under observation, and we are wondering, in view of the present occurrence, what is going to happen in that case. In that case operation was performed, using the Krönlein technic, and massive roentgen therapy was given after it. The report we received at the time of the operation, on a frozen section, was mixed cell sarcoma. That is why we proceeded with the massive roentgen therapy. Forty-eight hours afterward a second report was received, and this time it was mixed cell tumor. The young woman had a practically complete ptosis after operation; she refuses operation for this ptosis. I am not urging her. I should much prefer to let that alone for the time being. In this case a sequestrum is developing in the lateral wall of the orbit, and I should not be at all surprised if it becomes necessary to perform a sequestrectomy of that area of the zygoma.

Scleral Necrosis Associated with Periarteritis Nodosa: Report of a Case. CAPTAIN FRED HERBERT (MC), U.S.N., and LIEUTENANT (jg) SAMUEL D. MCPHERSON JR. (MC) U.S.N.R. (by invitation).

Periarteritis nodosa was first described by Rokitansky in 1852. In 1866 Kussmaul and Maier described the gross and microscopic pathology of the disease. Since that time more than 550 cases have been reported, and in only 10 per cent of these was ocular involvement exhibited (Urbach, E., and Gottlieb, P. M.: Allergy, New York, Grune & Stratton, Inc., 1946. Gaynon, I. E., and Asbury, M. K.: *Am. J. Ophth.* **26:** 1072-1076, 1943).

Goldsmith has recently reviewed the ocular signs of periarteritis nodosa (*Am. J. Ophth.* **29:** 435, 1946). These include papilledema with optic nerve atrophy; involvement of the choroidal vessels; involvement of the retinal vessels with the formation of fusiform aneurysms; retinitis with retinal detachment, hemorrhages and exudates; recurrent hemorrhages of the vitreous and involvement of the extraocular muscles (King, E. T.: *Tr. Ophth. Soc. U. Kingdom* **55:**246-256, 1935. Friedenwald, J. S., and Rones, B.: Ocular Lesions in Septicemia, ARCH. OPHTH. **5:** 175-188 (Feb.) 1931. Goldstein, I., and Wexler, D.:

Bilateral Atrophy of the Optic Nerve: A Microscopic Study, ARCH. OPHTH. **18:** 767-773 (Nov.) 1937. Böck, J.: *Ztschr. f. Augenh.* **78:** 28, 1932. von Hippel, E.: *Arch. f. Ophth.* **134:** 121-145, Böck, J.: *Ztschr. f. Augenh.* **69:** 225, 1929). A survey of the literature reveals no report of scleral necrosis occurring in the course of the disease.

REPORT OF CASE

G. H., aged 31, was first admitted to the United States Naval Hospital, Philadelphia, on April 11, 1946, with the complaint of weakness, headache and anorexia. The present illness apparently began two years prior to admission, when the patient, an enlisted man in the Army, had acute otitis media and abscess of the nasal septum. While under treatment with sulfonamide drugs, the patient manifested what was thought to be an allergic reaction to them. One blood culture out of many made prior to treatment was reported as positive for hemolytic Staphylococcus aureus. The patient recovered from this acute episode with considerable saddle-back deformity of the nose, due to loss of cartilage; chronic dacryocystitis on the right side, and deafness, necessitating use of a hearing aid. In February 1945 he had an interlobar collection of fluid in the right side of the chest and an exacerbation of the chronic dacryocystitis. Cultures of the pleural fluid yielded no pathogens, and inoculations of guinea pigs with the fluid were reported to give negative results. Both lesions cleared with penicillin therapy, and the patient was asymptomatic until just prior to the present admission.

Examination on admission revealed an interlobar collection of fluid in the right side of the chest, chronic dacryocystitis with fistula formation of the right, pronounced saddle-back deformity of the nose, large perforations of the nasal septum and advanced atrophy of all turbinate tissue, with nasal crusting and a tendency toward spontaneous epistaxis. The right ear drum membrane was conspicuously retracted, with recent vascularization, and the left drum membrane showed an old perforation with adherence of the margins of the tympanic membrane to the medial wall of the middle ear. Repeated examinations of the sputum were negative for tubercle bacilli, and careful study showed no evidence of active pulmonary infection. The patient desired a nasal plastic operation, and dacryocystectomy, with excision of the fistulous tract, was performed on May 1, 1946 as a preliminary to rhinoplasty and as a relief measure for chronic conjunctivitis. Vision was 20/20 in the right eye and 20/15 in the left eye, and no pathologic condition of the eyes was noted.

The immediate postoperative course was uneventful; the wound apparently healed by primary intention, and sutures were removed on the fourth postoperative day. At this time edema of the right eyelids developed. On the seventh postoperative day there occurred photophobia and lacrimation of the left eye and bilateral superficial punctate keratitis, which persisted in spite of local treatment with hot compresses and intravenous administration of typhoid vaccine. On the fourteenth postoperative day a spontaneous subconjunctival hemorrhage developed in the right eye at 1 o'clock, just outside the limbus. The following day this lesion became edematous, and a similar lesion appeared in the left eye. Within forty-eight hours both lesions ulcerated, and the

patient had spontaneous epistaxis. Smears and cultures were made of material from both lesions and were studied for aerobic and anaerobic bacteria, acid-fast bacilli and fungi. These were all repeatedly negative for organisms except for an occasional colony of diphtheroids. Direct scrapings were taken from both lesions and from the nasal mucosa and stained for tubercle bacilli and the common bacteria. These were likewise negative.

The conjunctival and scleral necrosis continued to progress until a "porcelain white," completely avascular, slough developed. The patient was treated with local application of penicillin drops and systemically with injections of 30,000 units of penicillin sodium every three hours. There was little change in his condition, although twenty-one days after the onset of the ocular disease an occasional vessel could be seen appearing in the area of the slough. One month after the onset the patient was given streptomycin, 2 Gm. daily for five days, with no apparent effect on the slowly healing process. After cessation of the streptomycin therapy, the patient became febrile, the temperature spiking to 99 to 100 F. at irregular intervals. Repeated cultures of blood taken during the febrile period were sterile.

At this time the eyes first showed definite evidence of improvement. Conjunctival epithelium began to cover the scleral sloughs, which had become so deep that uveal pigment could be seen shining through. At the same time, from the marginal conjunctiva, vessels began to invade the sloughing sclera and adjacent cornea to form a superficial pannus. At this time the patient complained of paresthesia in both hands and exhibited persistent eosinophilia, with a count of 8 to 10 per cent; albuminuria (1 to 3 plus), and microscopic hematuria. The sedimentation rate was 27 mm. in one hour. The Kahn reaction of the blood was negative, and examinations of the spinal fluid revealed nothing abnormal. In view of these findings, it was thought advisable to perform a biopsy of muscle to exclude periarteritis nodosa. This was done in the seventh week of the ocular disease.

Pathologic Report (Comdr. T. W. Bennett (MC), U.S.N.R.).—Sections from the gastrocnemius muscle were studied. In areas in the muscle fibers there was evidence of a low grade inflammatory change. In one area between the muscle fibers there were cross sections of several small blood vessels. These vessels were identified as arterioles. In one vessel, especially, the lumen was practically occluded. The intima appeared to be missing, and there was apparent thrombosis, with beginning canalization. About this area there was proliferation of connective tissue. Adjacent to the narrow area of connective tissue was a zone of round cells, polymorphonuclear leukocytes, plasma cells and occasional eosinophils. In another area there appeared to be complete thrombosis and organization, resulting in fairly dense fibrous tissue. About this area there was evidence of chronic inflammation. In another vessel proliferative changes appeared to be taking place in the intima and the subintimal area. About this area there was a moderate amount of chronic inflammatory change, characterized especially by the presence of plasma cells. It is believed that these sections represent three stages: beginning proliferative changes in the intima, complete thrombosis with occlusion of the vessel and complete thrombosis with beginning canalization of the thrombotic area. These

changes, it is believed, are consistent with those occurring in periarteritis nodosa.

In the eighth week of the ocular disease, redness, pain and swelling developed in the right ankle. This was considered to be due to vascular occlusion. This swelling was followed in the tenth week by a similar lesion of the left wrist. The lesion of the wrist suppurated, and exacerbation of the corneoscleral lesions occurred, the necrosis extending into the cornea. Prior to this time the ocular media were clear. Repeated examinations with the ophthalmoscope and the slit lamp failed to show any other pathologic condition. The vitreous now became hazy, and a beam without cells appeared in the anterior chamber eleven weeks after the onset of ocular symptoms. Shallow, necrotic ulcers developed on the buccal mucosa. Multiple vitamins, including riboflavin, failed to influence the course of the disease. Twelve weeks after the onset of ocular symptoms, intradermal nodules developed on both feet and legs. Biopsy of one of these nodules showed typical lesions of periarteritis nodosa. This diagnosis was confirmed by Dr. Arnold R. Rich, of Johns Hopkins Hospital. Details of the fundus were not visible. The margins of the original scleroconjunctival slough were not healed, but the central portion showed a thin scar with uveal pigment showing through. In the upper margin of the cornea superficial sloughs developed, which coalesced to form an ulcer, with an overhanging edge extending toward the central portion of the cornea in the manner of Mooren's ulcer. There was scattered superficial corneal vascularization. Both corneas became edematous. Several large keratic precipitates developed in the left eye. Vision was 1/200 in the right eye and 2/200 in the left eye.

Because the patient had responded to no other therapy, and in view of the previously reported positive blood culture for Staph. aureus, the patient was tested intradermally with staphylococcus toxin to determine his sensitivity. He was found to give a mildly positive reaction to 0.1 cc. of a 1 : 1,000 dilution and a strongly positive reaction to 0.1 cc. of a 1 : 100 dilution. With the latter dilution, a superficial slough developed at the site of injection. Intradermal desensitization with staphylococcus toxin in 1 : 1,000 dilution was given for about a month, with no evidence of favorable response, and he was discharged from the hospital, at his own request, fifteen weeks after the onset of the ocular disease.

A clinically similar type of ocular lesion has been described as anterior metastatic scleritis. According to Duke-Elder (Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2, 2062-2063) this is usually due to a staphylococcic embolus (90 per cent), but occasionally to pneumococci. In a few cases no organisms were found.

The fundamental pathologic change in periarteritis nodosa is inflammation of the medium and small arteries with fibrinoid hyaline necrosis and exudative processes. As the necrotizing process subsides in one organ it may involve another, with remissions and relapses. Many etiologic explanations have been suggested, but the most widely accepted one is that it is not a disease entity, but a hypersensitivity of the arterial walls. It is most often related to a bacterial allergy associated with chronic infection, but experimental evidence indicates

that drugs, foreign proteins and serums, and even foods or pollens, may be responsible. Since the widespread use of sulfonamide drugs, the number of cases reported has increased notably.

Hydration Properties of Excised Cornea and Factors Responsible for Transparency. DR. WILLIAM M. HART (by invitation).

Recent work (Cogan, D. G., and Kinsey, V. E.: *Science* **95**: 607-608, 1942) has emphasized the degree of hydration as the chief determining factor in transparency of the cornea, and as responsible for the optical difference between cornea and sclera. According to this concept, the cornea is endowed with a dehydrating mechanism to keep down its water content. When this mechanism fails, swelling occurs, and therefore opacification. The sclera, on the other hand, is always opaque because of the absence of any such mechanism. If, however, the sclera is deliberately dehydrated, as by being dried in air or placed in glycerin, it, too, becomes "transparent."

In the present study, swelling and transparency of beef corneas were noted in various buffer solutions, all of which were adjusted to the same osmotic activity (8.94 atmospheres) by adding dextrose. Throughout this study an absolute disparity was found between the degree of hydration and the turbidity of the cornea.

The cornea may be characterized as a lyophilic colloid system, inasmuch as it shows behavior analogous to gelatin and fibrin under like conditions. Like many specimens of gelatin, it has an isoelectric point of p_H 4.6, as shown by the swelling minimum.

Various factors were found to affect the transparency of the cornea independently of the water content. It is suggested that these factors operate by affecting the refractive index of the water or of the micelles or of both.

Affecting the micellar refractive index are the (1) temperature, (2) electrolytes, (3) isoelectric point, (4) dissociation, (5) association, (6) mechanical stresses (as in birefringence), (7) p_H, (8) hysteresis and (9) coacervate formation (due to protein-lipid-carbohydrate complexes). Affecting the refractive index of the water are the (1) p_H, (2) electrolytes, (3) nonelectrolytes, (4) surface tension and (5) temperature. According to this theory, when the refractive index of the solvent water in the cornea becomes very different from that of the particles, turbidity results.

The practical potentialities of these observations were shown in the fact that it was possible to clear the corneal opacities which occur spontaneously in cattle. Further work will be directed toward such an attempt in the intact animal.

DISCUSSION

DR. FRANCIS HEED ADLER: It would be difficult for any one to discuss this paper after hearing it for the first time, and it is quite impossible for me to do so, but I cannot refrain from mentioning how delighted I am that work of this type is being done here in Philadelphia. The results of investigations of this character do not remain long in the laboratory. They have definite practical significance.

A few years ago, Cogan, in Boston, and others began experiments on the permeability of the cornea and its property of imbibition, the

results of which are now applied in the clinic. They showed that the normal cornea soon becomes less transparent if bathed with a solution of isotonic solution of sodium chloride or with a hypotonic solution. In order to keep the cornea clear during an operative procedure, such as detachment of the retina, most surgeons now keep the cornea flushed with a saline solution of 1.5 per cent strength. These investigators also showed that most of the deleterious effect of cocaine solutions was due to their being hypotonic.

The question of turbidity of the cornea with loss of its transparency becomes increasingly important with the operation of transplantation of the cornea. For the last few years, Dr. Leopold has been interested in transplanting corneas from frozen dried material. Although these transplants take well, they soon become opaque and remain so. The answer to this is to be found in the kind of work which Dr. Hart is doing, and I trust that he will be encouraged to continue it.

DR. WILLIAM M. HART: I wish to thank Dr. Adler for his comment.

As shown in my data, the dehydrated cornea, when rehydrated, is often optically better than normal cornea. I was not aware of Dr. Leopold's work, of course, which was carried on under conditions of war secrecy, but the next point my associates and I had in mind was to try to transplant corneas from the dried state.

Opacity of the cornea is a common condition in cattle. We brought a number of such eyes to the laboratory. Some of them had deep ulcer craters, which I presume would be said to be scar tissue. We could clear such corneas in one of two ways: They could be dried in air, in which case they became clear as normal corneas, or we could let them swell in hydrochloric acid solutions of appropriate strength or in various buffer solutions. Corneas which have been dried may be rehydrated and do not then become opaque again.

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Brittain F. Payne, M.D., *Chairman*

Milton L. Berliner, M.D., *Secretary*

Nov. 18, 1946

INSTRUCTION HOUR

Malformations and Diseases of the Optic Disk. DR. RALPH I. LLOYD.

Dr. Lloyd presented a comprehensive review of cases, illustrated with lantern slides.

OBITUARY

James Watson White, M.D. DR. HAROLD W. BROWN.

Dr. James Watson White, long a prominent member of this society, died May 15, 1946, in his seventieth year. In 1905 he received his degree of Doctor of Medicine from Albany Medical College and was in general practice from 1905 to 1913.

Dr. White became associated with Dr. Alexander Duane in 1914 and remained with him until the latter's death, in 1926. The knowledge and understanding of the anomalies of the extraocular muscle which this association offered were soon expressed in Dr. White's authori-

tative discourses on the subject. It was with keen interest and an investigative mind that he continued with this important work and became an international authority on the subject. While Dr. White contributed many important and original observations in his lectures and writings, among which is "Recession of the Inferior Oblique," teaching was his greatest love.

For the past twenty-five years he had spent much of his time in collecting and devising teaching material and in organizing and actively teaching courses on the subject of anomalies of the ocular muscles in various medical societies and hospitals and at his office. He gave freely of his time and knowledge, carrying on an extensive correspondence with his students and colleagues, as a follow-up part of their work with him. He presented this difficult subject in such a vital and understandable manner that his regularly scheduled courses at the meetings of the American Academy of Ophthalmology and Otolaryngology, the New York Post-Graduate Medical School and Hospital and at his office were always in great demand. Many prominent ophthalmologists from every section of the country came to take his work. It was almost solely through his efforts that the important contributions of both Dr. Duane and Dr. White on ocular motor anomalies became of practical use to so many ophthalmologists.

He was a sincere and truly great clinician and teacher, sparing no effort to help the individual student. His now familiar "Dr. White's Diagnostic Card" was originally designed to clarify the diagnostic position of the eyes to a single member of a relatively large class. With students he was practical, patient and considerate and showed an appreciation of their need and an ability and willingness to help. He had the insight and broad, comprehensive viewpoint of a great humanitarian.

As a person, Dr. White was considerate, generous and friendly and possessed a fascinating wit and sense of humor. He had a unique and natural approach to people that was immediately disarming, and he was loved by all who knew him. In the clinics or at his office, the observer never ceased to wonder at the ease with which he immediately gained the affection and cooperation of children. Not only ophthalmologists, but all who had the privilege of his friendship, have suffered a great loss in his death.

REPORT OF CASES

Therapeutic Sulfadiazine Poisoning with Pemphigoid Lesions: Conjunctival Signs. DR. BENJAMIN FRIEDMAN.

This paper will be published in a future issue of the ARCHIVES.

DISCUSSION

QUESTIONS FROM THE AUDIENCE: What was the end result in vision? Did the man whose case is described have any record of inoculation? Were any cultures made of the contents of the vesicles? Did the question of smallpox arise during the examination?

DR. BENJAMIN FRIEDMAN: The conspicuous feature of these cases was that the cornea was never attacked. For that reason, the end results were easy to distinguish from those of trachoma, in which the cornea becomes involved and vision is often affected. Likewise, it differentiates this disease from the particular type of erythema

(Stevens-Johnson disease) which affects the cornea in a severe manner. The condition in these cases was not the result of smallpox. The cutaneous lesions were described by the dermatologists as characteristic of pemphigus. In all the cases a misdiagnosis either of measles or of scarlet fever was made. That, of course, is easy to do in a large military establishment, because the personnel are primarily on guard against contagious diseases, and when there is any rash which simulates a contagious disease the patient is immediately treated for such. The longer these patients were treated with sulfonamide drugs the worse they became, and this particular patient nearly died as a result of the drug poisoning. The Navy reserves the name of therapeutic poisoning for cases in which there is an untoward reaction to any drug.

Fundus Oculi as an Indicator of Vascular Damage in Diabetes Mellitus. DR. HENRY DOLGER.

The twenty-five years since the discovery of insulin have witnessed a mounting incidence of degenerative changes in all diabetic patients. Wagener reported a "steadily increasing frequency of retinopathy, especially in the younger age groups" (in 76 per cent of patients under 30 who had had diabetes more than ten years).

His claim that the duration of diabetes is more important than the age of the patient is corroborated in the present study. Careful scrutiny of the retina of each patient over the course of years indicated that the earliest clinical manifestation of vascular damage can be found in the eye. This was especially true in 55 patients with "juvenile diabetes" in whom hypertension and albuminuria were noted after the typical retinal hemorrhage had occurred.

Within a period of a twenty-five years' duration of diabetes, not 1 of 200 patients examined regularly escaped retinal hemorrhage, regardless of age of onset, severity of diabetes or type of treatment used.

Retinopathy usually presaged progressive vascular degeneration. Fifty per cent presented hypertension and albuminuria at the time of the earliest retinal hemorrhage.

Present day treatment of diabetes has failed to avert the accelerated vascular damage which is an associated phenomenon of the disease, and not a "complication."

DISCUSSION

DR. BRITTAIN F. PAYNE: As diabetic hemorrhage is a matter of general concern to ophthalmologists, may I ask what effect, if any, does vitamin C have on the absorption of diabetic hemorrhages?

DR. CONRAD BERENS: Has Dr. Bolger had any experience with vitamin P (rutin; hesperidin)? I have wondered whether patients who showed increased capillary fragility might be benefited, whereas those who did not show increased capillary fragility might fail to be benefited.

DR. MARTIN COHEN: Has Dr. Dolger had any experience with lipemia retinalis, which is pathognomonic of diabetes; and how does he account for the fact that there are no hemorrhages in this condition and no degeneration of the vascular wall? Is the latter condition the factor?

DR. JOSEPH J. FRIED: Did Dr. Dolger mention the diagnostic importance of capillary aneurysms and phlebosclerosis as the first manifestations in the eyegrounds in cases of diabetes in which there are no hemorrhages? This is thought to be of considerable importance from the diagnostic and the prognostic point of view, as these signs point to general vascular damage before any routinely known signs of diabetic retinopathy are present.

What is Dr. Dolger's clinical experience in such cases? Also, what is his experience with hesperidin—vitamin P, or recently better known as rutin? This therapy was lately recommended in cases of diabetic retinopathy to counteract increased capillary permeability and increased capillary fragility.

PROF. W. J. B. RIDDELL, Glasgow, Scotland: I have nothing to add, except to refer to the work of my predecessor in Glasgow, Professor Ballantyne, who has been interested for many years in diabetic retinitis. Dr. Fried has spoken of the aneurysms, which Dr. Ballantyne was the first to describe, and as to the significance of which I think we agree.

DR. HENRY DOLGER: Vitamin P, "citrin," rutin and hesperidin are similar substances, flavone glucosides of varying degrees of purification. Neither vitamin C nor vitamin P, rutin nor hesperidin influenced retinal hemorrhages significantly and unequivocally. Evaluation of such therapy is difficult because of the spontaneous remissions and exacerbations displayed by these lesions. The retinopathy is not a vitamin deficiency but a fundamental alteration of the intracellular oxidative enzyme systems. The work being done with cytochrome C, or related oxidative enzymes, by which one is able to maintain the visual threshold during anoxia, is far more provocative and pertinent than vitamin research. Because of this more promising approach, I have given up hope in the use of rutin and hesperidin with vitamin C. My results with these agents have not been strikingly different from the spontaneous improvement often shown by a group of untreated control patients. Whether vitamin C is given by intravenous injection or orally seems immaterial. A number of these patients have had repeated determinations of the ascorbic acid level of the blood and, although no value was below normal, the lesions recurred or disappeared without any evidence of vitamin C deficiency.

This brings up the question of capillary fragility. The tourniquet test has no bearing on the ocular lesion. In patients with normal or high vitamin C levels of the blood in whom I could observe the appearance of repeated hemorrhages, the capillary fragility test proved so variable as to be valueless. It might be positive one day, negative within twenty-four hours and positive again a week later. The erratic behavior of the tourniquet test week after week in the same patient could not be correlated with associated changes in the retina. In the main, as the retinal lesions advanced inexorably, the test remained positive despite intensive therapy. I do not believe that the tourniquet test measures anything but the integrity of the intercellular cement in capillary walls, and therefore more delicate alterations of function in these structures cannot be estimated by present methods.

Lipemia retinalis has nothing to do with this vascular lesion. It is a hang-over from the days when patients were on high fat diets and lipemia was more common. The lesion I am discussing is a vascular one and is related to the capillary aneurysms described by Ballantyne. I feel that this controversy of whether or not aneurysms exist has almost a religious bias. I believe that persons who are unbiased and who examine the eyegrounds repeatedly and early cannot help but find them, especially in younger patients with diabetes of some duration. Except for the occasional chance finding of the early lesions of capillary aneurysm and retinal hemorrhage, the opthalmologist is privileged to see only the later stages of diabetic retinopathy. Only by the diligent and repeated scrutiny of the retina throughout the course of the diabetes will the true pathogenesis of this tragic complication be understood.

PAPER OF THE EVENING

Hereditary Anomalies of the Eye (Charles H. May Memorial Lecture).
PROF. W. J. B. RIDDELL, Glasgow, Scotland.

This general title has been chosen to cover a few of the common hereditary anomalies of the eye in which I have been interested as a clinician. Certain conditions, such as color blindness, are clearly hereditary and are not influenced by the environment of the patient. Myopia is probably under more genetic than environmental control, whereas infections are conditioned to a greater extent by environment, but families with low resistance to common infections are well known. Injuries are largely due to environment, although persons with blue scleras are more liable to break their bones than are normal people.

Modern genetic theory is a particulate one, concerned with the twenty-four pairs of chromosomes which are known to exist in man. The determining factors or genes are assumed to exist within the chromosomes like beads on a string. Two conditions having no pathologic connection, such as hemophilia and color blindness, may be inherited through genes carried on the same chromosome or on opposite members of the same pair of chromosomes. I have traced out the segregation of these two anomalies in certain families. The pooled data from other such pedigrees have made it possible to express the position of the genes as a linkage relation. Recent work has added considerably to knowledge of this problem, and it is now possible to envisage the creation of human chromosome maps. The collection and publication of material suitable for such studies may add to scientific knowledge, and it is a field open to any trained clinician; in fact, he may be at a greater advantage in such work than a pure scientist.

Book Reviews

Optical Transplantation of the Cornea and Tissue Therapy. By Academician V. P. Filatov. Price, 31½ rubles. Pp. 232. Moscow: Markomzdrav, State Publishers of Medical Literature, 1945.

This book by the distinguished Russian pioneer in corneal transplantation is a summary of his previous work on corneal transplantation and tissue therapy. It is divided into two parts: (1) corneal transplantation and (2) tissue therapy.

In the first part he discusses the history of keratoplasty, the classification of corneal transplantation according to the therapeutic requirements, the condition of the leukoma and the indications for and the technic of partial penetrating corneal transplantation. The Filatov-Marzinkowsky trephine is described, with illustration, and its advantages are evaluated. A special spatula connected with Filatov's trephine prevents the injury of the lens and prolapse of the vitreous. The complications (of which the most frequent is glaucoma in the postoperative period) and the material for corneal transplantation are discussed in another chapter. Filatov has been using material from the cadaver, the eye being enucleated two to twelve hours after death and preserved at a temperature of 2 to 4 C. for from one to three days.

A total of 842 keratoplasties were performed by Filatov and his co-workers from 1922 to 1941 (a number of transplantations done during wartime are not included). In 171 operations the cornea was taken from the living person and in 671 from the cadaver. Successful results were obtained in 24.1 per cent of the first series (cornea from the living eye) and in 66.6 per cent of the second series (cadaver cornea). (These data include favorable cases only.) The author thus prefers the use of preserved cornea from the cadaver because of the better results. He states that corneal transplantation has proved that homoplasty in the human cornea is possible. Improvement of the leukoma by additional transplantation of transparent corneal elements is the content of another chapter. Filatov believes that this improvement is brought about by rearrangement of the corneal elements and that clearing of the leukoma is effected by biogenic stimulation.

The experimental and pathologic study of the transplant occupies an important place at the Odessa Experimental Institute of Ophthalmology (some eyes with corneal transplantation were removed after the death of the patient, and some eyes were enucleated because of painful glaucoma). This investigation indicates that a true union of the transplant takes place and that regeneration of the corneal elements from the periphery of the cornea does not occur. A study was made of the corneal transplant, its nutrition and the effect of preserving it at various temperatures and in various mediums. It was found that the cornea was preserved best per se, without any fluids, at a temperature of 3 C. It was also found that the oxidation processes were preserved both in the cornea and in the lens; i. e., despite the autolysis,

the viability of these tissues was maintained. The cornea preserved at a temperature of 2 to 4 C. showed a direct division and growth of the cells; i. e., growth of corneal cells in the tissue was obtained at a low temperature, constituting a new phenomenon.

One hundred and thirty-four photographs illustrate the favorable results of keratoplasty with use of cadaver cornea preserved at a low temperature. Vision was improved in the eyes so treated from counting fingers to from 0.03 to 1.0. The time of observation was from seven months to three or four years.

In the second part, tissue therapy is discussed. Tissue therapy took its origin from keratoplasty. In 1933 Filatov began to use transplantation of clear corneal tissue when the transplants became opaque and obtained a clearing of the original transplant. He uses the cornea preserved at a low temperature, as such transplants evidently contain substances which stimulate and accelerate the regenerative power of the corneal tissue of the recipient. He emphasizes the use of preserved tissue as essential and as the basis of tissue therapy. Filatov explains the salient points of tissue therapy as follows:

Under certain conditions any animal tissue undergoes biochemical transformation and forms active substances, which Filatov calls "resistance substances," or "biogenic stimulators." These substances stimulate biochemical processes in the tissues in which they develop. Low temperature appears to be an unfavorable condition for animal tissues and darkness for green leaves. Thus, tissues preserved at a low temperature or leaves of aloe kept in darkness for fifteen days are rich in biogenic stimulators. If such tissue is introduced into the affected organism (by implanting a piece subcutaneously or injecting an aqueous solution), it stimulates the regenerative qualities of the organism and increases the cellular metabolism, and thus aids the recovery of the organism.

Filatov and his co-workers have been using the following tissues: cornea, conjunctiva, skin, placenta and extracts of placenta, as well as injections of cod liver oil. Leaves of aloe preserved in the dark for fifteen days at a low temperature is the plant tissue used. These tissues sterilized in the autoclave at a temperature of 120 C. for one and one-half hours do not lose their biogenic stimulating quality. The tissues are implanted either under the conjunctiva or into the skin of the abdomen. Cod liver oil is given intramuscularly, 1 to 2 cc. every other day, for from ten to fifteen injections.

Tissue therapy was applied in a great number of diseases of the eye, namely: opacification of the transplant, 16 cases; interstitial, tuberculous, scrofulous, rosacea and herpetic keratitis, 117 cases; corneal ulcer, 23 cases; uveitis, 23 cases, and retinitis pigmentosa, 110 cases. In cases of the last condition injections of cod liver oil, implantation of preserved liver tissue into the skin or implantation of placenta under the conjunctiva was used. In 180 cases of trachoma and in a number of cases of optic nerve atrophy tissue therapy was of benefit. The best results were obtained in cases of keratitis and uveitis.

Tissue therapy was also applied in relief of various other diseases, such as lupus of the skin of the face and mucous membranes and

psoriasis. In all these cases the disease was of long standing and did not respond to routine therapeutic measures. Good results were obtained with inflammatory conditions of the female pelvis and its organs. Tissue therapy gave beneficial results in cases of poorly unified fractures of bones, contractures of joints, tuberculous arthritis (without fistulas), inflammation of the sacroiliac joint and myositis.

The book contains a wealth of material, with histories and photographs of patients and illustrations of the technic.

A great deal of experimental work has been done, and such investigations are still going on in several laboratories for the evaluation and improvement of methods of tissue therapy. This book does not lend itself to abstracting, particularly the experimental parts. A translation would be useful for the English-speaking ophthalmologist.

OLGA SITCHEVSKA.

Ocular Prosthesis. By J. H. Prince. Price, $4. Pp. 184, with 71 illustrations. Baltimore: Williams & Wilkins Company, 1946.

The production and fitting of ocular prostheses have become more important with the introduction of new materials and with an increase in the need of artificial eyes. A quarter of a million people in this country wore prostheses before the war, and the number has significantly increased. This monograph, written by a member of the British Optometric Society, is a summary of earlier methods and a brief introduction to improved forms made possible by chemical advances.

The first seven chapters discuss the history of artificial eyes, the anatomy and physiology of the orbit and clinical fitting. The final chapter is an elementary presentation of the materials and methods of manufacture.

Polished stone or gold implants were originally used. These were chemically and esthetically unsatisfactory and were rapidly replaced with the introduction of glass, made in molds or by blowing. Various formulas have been used in making glass that is durable, colorable and resistant to tears and the secretions of the residual mucous membrane; silicon dioxide is mixed with varying amounts of common light metals and with aluminum, lead, fluorides or titanium for resiliency and tinting.

Since glass is breakable and difficult to manufacture in a large series of colors and sizes, plastic materials have lately been used. Methylmethacrylates, of the acrylic ester group, have proved most successful. In actual manufacture, a mold of the indicated size is made with dental stone and placed in a press. Acrylic monomer and polymer, with suitable colorings, are mixed, placed in the mold and heated. An iris is then put on the scleral shell with paints or by photogravure, and a cornea of clear acrylate is added. Such a prosthesis is light, relatively immune to ocular secretions and esthetically pleasing.

The presentation is uneven both in its clinical and in its manufacturing aspect; for example, there is no mention of spontaneous explosion of glass eyes, sympathetic ophthalmia or basket implants. Nonetheless, this small book is an informative introduction to a subject of increasing significance to ophthalmologists.

LLOYD MILLS JR.